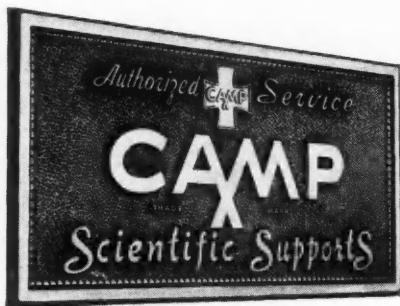


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# California MEDICINE

OFFICIAL JOURNAL OF THE CALIFORNIA MEDICAL ASSOCIATION  
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VOL. 69

AUGUST, 1948

No. 2

## Q Fever in Artesia, California

FRANK W. YOUNG, M.D., *Artesia*

IN the area around Artesia, California, a region of about 12,000 population in southeastern Los Angeles County where dairying is a principal industry, outbreaks of fever in humans were noted following arid spells and windstorms last year. These outbreaks, which followed with almost predictable regularity and within four or five days after the so-called Santa Ana windstorms, were ascribed variously to influenza, virus pneumonia, primary atypical pneumonia, and infection of unknown origin. The salient clinical features were severe and persistent headaches, fever with little matinal remission, rigors, generalized malaise and occasionally pneumonia with a paucity of clinical findings as confirmation.

The similarity of conditions in Artesia to those in Amarillo, Texas, where the epidemic of 1946 caused nation wide interest, suggested the possibility of Q fever, and for this reason blood from 14 patients was sent to the National Institute of Health in Bethesda, Maryland. Reports on eight were returned strongly positive for Q fever. In these cases the patients' temperature returned to normal in from one to three weeks. One of the remaining blood specimens was slightly positive and five were negative. (It should be noted that the negative report on those five patients, who had acute symptoms, is not conclusive, since the complement fixation test does not develop a positive reaction in the acute states of the disease.)

The fact that there was positive reaction in eight of the fourteen specimens of blood permits assumption of a clinical diagnosis of Q fever in 20 or 30 similar cases in which the patients' blood was not tested but in whom the onset and course were similar.

### CLINICAL DATA

Figures 1 and 2 are roentgenograms of the chests of two patients hospitalized, and these films were diagnosed by the roentgenologist as characteristic of primary atypical pneumonia.



Figure 1

Blood-tinged sputum was observed in several cases, including the two in which the patients were hospitalized, and without exception in those patients in whom the course of the disease was prolonged. It is reasonable to assume pneumonic infiltration in the patients who were not hospitalized.

The erythrocyte count, hemoglobin determination and leukocyte count all were essentially within normal range. Albumin and granular casts were observed in the urine of a few patients in whom the febrile course was unusually stormy.

The fever ranged from 101° to 105° F. with little remission in the severe cases, and the intensity of headache and malaise paralleled the febrile course.



Figure 2

Headache was bitterly complained by most of the patients. After convalescence, however, the discomfort was seldom remembered. This observation has been corroborated by Dr. Charles S. Shepard of the rickettsial research unit of the National Institute of Health. This amnesia for the discomforts experienced during the stormy course of the disease would suggest possible encephalitic cellular changes.

Spinal fluid examination was not done in any case but a thorough examination of the nervous system disclosed no abnormalities.

Treatment in all cases consisted of penicillin injections, 200,000 units daily, with sulfadiazine by mouth, 6 gm. daily in divided doses. This combination seemed to have a salutary effect, but evaluation of it was difficult because of the marked variance in the course of the disease.

In the cases not complicated by pneumonic invasion the patients usually were afebrile in three to seven days. In a few instances morphine sulphate hypodermically in doses of 0.03 gm. (Gr. 0.5) was necessary to alleviate discomfort. Para-aminobenzoic acid was not used.

#### COMMENTS

All reported cases of Q fever which occurred during the explosive outbreak in March in Amarillo, Texas, were among workers in three places associated with the handling of live stock. In Artesia and its environs the cases were catholic in distribution. One positive reaction to the complement fixation test was obtained in the blood of a ten year old schoolgirl, another in blood of a fourteen year old high school freshman, and still another in blood from a housewife whose husband was a mechanic in a garage.

The fact that definitely proved cases of Q fever followed so closely upon dust storms in the Artesia area would seem to question the accepted proposition that the incubation period of the disease is 14 to 26 days. It is the author's opinion that Q fever is much more prevalent than hitherto believed. Also, it is suggested that *rickettsia burneti* is indigenous to dust in the vicinity of cattle barns and corrals, and is disseminated by winds following arid spells. These atmospheric conditions existed in Artesia immediately before outbreak of the epidemic. The opinion is expressed that the disease may be contracted without direct contact with cattle.

1442 Pioneer Boulevard.

## Q Fever in California

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IN 1935 there occurred among packing house workers in Brisbane, Australia, a number of cases of an obscure febrile illness. Derrick,<sup>15</sup> who investigated the outbreak, recognized that it represented a disease previously undescribed, and tentatively named it "Q" fever, the name by which it is still known. This new entity was found to belong to the rickettsioses<sup>5</sup> and the causal agent was designated<sup>16</sup> as *Rickettsia burneti* (now known as *Coxiella burnetii*; vide infra).

Meanwhile, in the United States a filtrable agent was isolated by Davis and Cox<sup>13</sup> (1935) from ticks (*Dermacentor andersoni*) collected in the Nine Mile Creek area, about 30 miles west of Missoula, Montana. The agent was identified as a rickettsia and because, unlike other members of this group, it was readily filtrable, it was named *Rickettsia diaporica*.<sup>11</sup> Its role, if any, in the causation of human disease was unknown, but its pathogenicity for man was subsequently revealed when an accidental laboratory infection occurred.<sup>19</sup> Laboratory studies on this case suggested<sup>19</sup> that the infection was related to Australian Q fever; later, detailed immunologic investigations<sup>2, 6, 20</sup> proved that *R. burneti* and *R. diaporica* are essentially identical, and that the "Nine Mile fever" of Montana and the Q fever of Australia are the same disease.

Until 1944, Q fever was considered to be a disease confined to Australia and the United States. Then, between November, 1944, and June, 1945, there occurred eight outbreaks, totaling approximately 600 cases, among allied troops stationed in Northern Italy, Greece and Corsica.<sup>31</sup> In addition, there was an explosive outbreak involving approximately one-third of a group of 1,600 troops returning to this country from Southern Italy.<sup>8</sup>

Q fever was reported from Panama<sup>7</sup> in 1946 and from Switzerland in 1947.<sup>22</sup>

Prior to 1946 naturally acquired Q fever appeared to be rare in the United States. Several outbreaks of atypical pneumonia studied prior to 1944 gave no evidence that *R. burneti* was involved,<sup>17, 38</sup> and the only authentic case was that described by Hesdorffer and Duffalo<sup>23</sup> in Montana (1941). The probability that the disease may be widespread, however, had been suggested by Cox,<sup>12</sup> who found specific antibodies in the sera and/or isolated the rickettsia from 19 patients from Idaho, Montana, Wyoming, Nebraska, Nevada, Oregon, and Washington.

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Read before the sections on Public Health and General Practice at the 77th Annual Session of the California Medical Association in San Francisco, April 11-14, 1948.

\*According to a personal communication from Dr. Derrick, the "Q" stands for "query" rather than "Queensland."

In March, 1946, the first known naturally occurring outbreak of Q fever in this country appeared explosively at Amarillo, Texas, when 55 cases, with two deaths, occurred among the 136 employees of three packing houses.<sup>36</sup> In August of the same year another outbreak occurred, this time at a Chicago packing house where 33 of 81 men on a killing floor were affected.<sup>34</sup>

In May, 1947, the presence of the disease in California was uncovered by Dr. Frank Young of Artesia, who suspected that some of the unusual pneumonias he was encountering might be due to *R. burnetii*. (See page 89, this issue.) Serologic tests at the National Institute of Health confirmed his clinical impressions, and a rapid survey made by the United States Public Health Service revealed that the disease is endemic in Southern California. A field laboratory for the study of the epidemiology of Q fever was established at Hondo on the property of the Rancho Los Amigos, and staffed with personnel from the United States Public Health Service and the California State Department of Public Health. The investigation is a joint project of the National Institute of Health, the California State Department of Public Health, the Los Angeles City and County Health Departments, and the California State Department of Agriculture.

### ETIOLOGY

The causal agent of Q fever is, as already mentioned, a rickettsia which etiologically, therefore, places this disease in the group to which belong epidemic and murine typhus, scrub typhus, Rocky Mountain spotted fever, boutonneuse fever, and the newly described rickettsialpox. Morphologically and tinctorially, *Rickettsia burnetii* resembles the other rickettsiae, but it is of interest that in certain other respects it differs from them. Thus, the organism is filtrable;<sup>5, 11</sup> it forms large microcolonies (strikingly similar to those seen with psittacosis virus) in infected cells in the mouse spleen;<sup>5, 9</sup> it produces no soluble antigen,<sup>37</sup> nor does it produce agglutinins to the "X" strains (OXK, OX2, and OX19) of *B. proteus*;<sup>5, 12, 15</sup> also, the rash seen with other rickettsial diseases is absent in Q fever.

Because of these striking characteristics which set off the Q fever organism from the other rickettsiae, it was proposed by Bengtson, Steinhaus, and others (see, for example, Philip<sup>30</sup>), that the organism be placed in a new genus to be known as *Coxiella*, the genotype to remain the same. This has been accepted and *Rickettsia burnetii* Derrick now becomes *Coxiella burnetii* (Derrick), and is so listed in the latest (1948) edition of Bergey's Manual of Determinative Bacteriology.<sup>3</sup> The new terminology, therefore, will be used from this point on in the present discussion.

## CLINICAL ASPECTS OF Q FEVER

**Onset.**—The incubation period is from 14 to 32 days,<sup>31,34</sup> with an average of about three weeks. The onset may be abrupt,<sup>32</sup> or may be gradual,<sup>21</sup> the proportion of cases in either category varying with the outbreak. In general, the illness appears to be more severe if onset is sudden.

The initial symptoms are predominantly constitutional and there are few or no symptoms referable to the respiratory tract. Presenting complaints are headache, feverishness, sweats, chilly sensations, muscular aches, chest pain, tiredness, and anorexia.

**Symptoms.**—Headache, frontal or occipital, is the most frequent symptom; it varies greatly in severity but generally is one of the major complaints. Chilly sensations are common, but true rigor is seldom seen.<sup>21,32</sup> Generalized malaise is frequent, as are muscular aches and pains; the latter may be quite marked and if in the nuchal area may lead to a suspicion of meningitis. Retro-orbital pain is also a common complaint. Photophobia may occur, but is rare. Anorexia of variable degree is encountered during the febrile stage, and nausea and vomiting are present in some cases.

Respiratory symptoms such as nasal stuffiness or discharge, sore throat, and sneezing, are generally minimal, if present. Cough also may be absent, but generally appears about the fifth day and is slight and dry; in about one-third of the cases the cough is productive.

Chest pain occurs in one-third to one-half of the patients; it may be mild, brought about by deep inspiration or coughing, may be a dull ache or a feeling of oppression in the chest or, occasionally may be a true pleuritic pain.

**Physical findings.**—The physical signs in Q fever, as in the so-called atypical pneumonias of viral origin, are few.

There is fever ranging from 101°F to 105°F, and the patient is flushed and appears acutely ill. The nasal and pharyngeal mucous membranes may be injected or congested, but this is seldom marked. The pulse rate rises with the temperature, but there is a relative bradycardia. The respiratory rate is normal.

Abnormal physical signs in the chest may be present, but are seldom very obvious. Slight diminutions in breath or voice sounds, decreased tactile fremitus, and friction rub occasionally may be detected, and there may be some localized dullness over a pneumonic area. Coarse rales or rhonchi are unusual. Most frequently encountered are very fine crepitant rales, heard best at the end of deep inspiration. These are usually transient, persisting for only a day or two, and so may be missed unless looked for; in some instances they are present over a period of a week or more.

**Course.**—The disease is variable in severity and there is little correlation between severity and the amount of pulmonary involvement. The temperature returns to normal within a seven to ten day period on

the average. With defervescence, the symptoms disappear in the moderately ill, but weakness and fatigue on slight exertion may persist for several weeks in those with a severe attack. Some loss in weight occurs in the more severe cases. Relapses have been described.<sup>18</sup>

**Clinico-pathologic findings.**—The erythrocyte count and hemoglobin concentration are normal. Leukocyte counts are normal or a little low, ranging from 4,000 to 10,000. The blood sedimentation rate is increased during the symptomatic period and returns to normal when the patient is asymptomatic. Results of urine examinations are negative.

Roentgenologic studies of the chest almost always reveal the presence of some patchy consolidation, usually involving only one lobe, but sometimes more. The lower lobes are the most frequently affected, but any lobe may be involved. The lesions appear on the third or fourth day, are located peripherally and have a homogeneous, ground-glass appearance. They increase in size by extension to reach the maximum at about the time the patient becomes afebrile (seven to ten days), then regress slowly, sometimes persisting for days after the patient has otherwise completely recovered.

## DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The symptoms in the early stages of Q fever are no different than those encountered in many other febrile conditions and afford no means of distinguishing this disease from others such as influenza, brucellosis, the enteric fevers, and meningitis, to mention only several; the usual laboratory examinations also provide no assistance.

Pulmonary involvement may later be suspected from the physical findings, but is best demonstrated, or confirmed, by roentgenograms of the chest. The presence of pneumonitis leads generally to a diagnosis of "atypical pneumonia," which, it might be pointed out, is a clinical syndrome, not a disease entity with a specific etiology. If a definite diagnosis based on etiology is to be achieved, consideration must be given at this stage to the diverse agents which can produce this picture. Among these, in addition to the Q fever rickettsia, are various bacteria (pneumococcus, streptococcus, staphylococcus, Friedlander's bacillus, tubercle bacillus) the fungi (*Monilia* sp., and *Coccidioides immitis*), and the viruses of influenza, lymphocytic choriomeningitis, and especially those of psittacosis and ornithosis. (There exists, however, a large residuum of cases in which the specific cause of the pneumonitis cannot be resolved;\* these have been classified by the Army Commission<sup>18</sup> as "primary atypical pneumonia, etiology unknown," and it is in this group that the cold hemagglutination phenomenon is encountered.)

The bacterial pneumonias are differentiated by leukocytosis, presence of specific organisms in the

\*Eaton and his associates (see the excellent review by Melkjohn<sup>35</sup>) have presented evidence, however, that more than one-half of the cases in this category are due to a virus which they have isolated on a number of occasions and to which the patients develop neutralizing antibodies.

sputum, and response to chemotherapeutic or antibiotic agents.

A fungal factor in the etiology is demonstrated by the presence of the fungus in the sputum, and in the case of coccidioidomycosis, by serological and skin tests.

Influenza is associated with upper respiratory disease symptoms, but isolation of the virus or serological tests are required for absolute certainty.

Cases due to the virus of lymphocytic choriomeningitis or those of the psittacosis group are diagnosed by serologic methods, or by isolation of the specific virus from sputum or blood, or from tissues post-mortem. A history of contact with birds may point to psittacosis or ornithosis, but the diagnosis should be confirmed by laboratory methods.

A definitive diagnosis of Q fever is made by isolation of the rickettsia through inoculation of blood into guinea pigs or by showing that complement-fixing antibodies develop during the illness. *It should be emphasized here that for the serological diagnosis of rickettsial and viral diseases, two specimens of blood, one taken in the early, acute stage of the illness and a second taken later in the convalescent phase, are required since diagnosis depends upon the demonstration of the appearance or rise in titer of specific antibodies.* Agglutinins to the X strains of *B. proteus* are not evoked in this disease, and hence the Weil-Felix test is of no aid in diagnosis.

#### TREATMENT

Therapy is entirely symptomatic and supportive. Sulfonamides and penicillin have no effect on the course of the disease. Streptomycin has been reported<sup>25</sup> to lower the mortality rate of guinea pigs inoculated with *Coxiella burnetii*, but its usefulness in human infections is unknown.

#### EPIDEMIOLOGY

With the discovery that Q fever is a rickettsial disease, and with the knowledge that the other rickettsioses are transmitted by arthropods, a search early was made for possible arthropod vectors of this disease. The occurrence of naturally-infected ticks has been reported from Australia (*Haemaphysalis humerosa*);<sup>35</sup> the United States (*Dermacentor andersoni* (*Montana*)<sup>13</sup> and *Wyoming*)<sup>14</sup> *D. occidentalis* (West Coast States<sup>27</sup>) and *Amblyomma americanum* (Texas<sup>29</sup>); and Morocco (*Hyalomma savignyi*),<sup>4</sup> but clinical and epidemiologic studies have failed to incriminate this arthropod, or any other, in the transmission of Q fever to man.

The work of the Australian investigators indicates that Q fever is primarily an infection of bandicoots (a small marsupial) and cattle, among which it is disseminated by ticks; the human disease represents only accidental infections, arising outside, and not necessary to, the maintenance of the basic cycle, and presumably is acquired by inhalation of dried tick excreta on the hides of cattle. This would explain the high incidence of the disease in those whose occupation brings them into contact with cattle, and seems to be the only explanation for the cause of

such outbreaks as that at Amarillo. Similarly, in the Italian outbreaks, dust, either that in the quarters as a whole or from hay and straw used for bedding, appeared to be the most likely source of infection; since various birds and animals shared the buildings with the human tenants, it is not impossible that the dust was contaminated with excreta from infected birds or animals or their ectoparasites. Finally, the only logical explanation for the several laboratory outbreaks<sup>10, 24, 33</sup> is that the agent was air-borne. Person-to-person transmission apparently does not occur.<sup>31</sup>

Epidemiologic studies initiated in Los Angeles County by Shepard and Huebner of the National Institute of Health following the discovery of the disease in that area indicated that many cases were in persons occupationally associated with cattle (livestock handlers, dairy workers). Serologic studies on cattle revealed that many possessed antibodies to *Coxiella burnetii*—e.g., 12.5 per cent of 1050 animals in one herd, approximately 30 per cent of 90 animals in another<sup>26</sup>—indicating that these animals had been or were infected. Inoculation into guinea pigs of single or composite milk samples pooled from random strings of cows gave evidence that 40 of the 50 specimens tested were infected,<sup>26</sup> a remarkably high proportion. Since, according to serologic surveys, infection is geographically widespread among the cattle population, and as the milk, much of it raw, is widely distributed in the same area, some relationship between these factors and human infection is suggested. Ingestion of infected milk has been tentatively considered as a possible cause of the human disease, but the evidence thus far is not conclusive, first because of insufficiency of data and, second, because of findings that in certain groups of individuals this mode of transmission was improbable. On the other hand, it remains to be proved that infected milk plays no role in the epidemiology of the disease—infection may be acquired through some route other than the oral.

To date, approximately 200 cases of Q fever have been diagnosed in California. Practically all have been in Los Angeles County, but single cases have been diagnosed serologically in Santa Barbara, Ventura, and Orange counties.

At the present stage of the study, there is no indication of seasonal differences in the occurrence of cases, but a much longer interval of observation is necessary before a valid judgment can be reached. The age of the patients ranged from 3 to 75 years,<sup>1</sup> the majority coming within the 20-44 year old group. Males were affected more frequently than females, the ratio being 4 to 1. Both the age and sex distribution, however, presumably will have to be revised as more information is acquired, since the present figures are derived in large part from certain groups with occupational exposure to livestock (packing houses and dairies).

The Viral and Rickettsial Disease Laboratory of the California State Department of Public Health has just recently demonstrated the presence of antibodies to *C. burnetii* in the convalescent sera of four individuals residing in Northern California (Solano,

Yolo, Glenn, and Plumas counties), and giving a history of a recent febrile illness. In addition, a clinical case of Q fever in a patient in Stanislaus County was investigated, and serologic studies disclosed that all the six other members of the patient's family also possessed Q fever antibodies. There has been no opportunity as yet to investigate epidemiologically any but the Stanislaus County cases. In these, it was possible to rule out exposure to the disease in Southern California, and it appears that infection was acquired locally. It is of interest that while only 1 of 26 cattle on the ranch possessed demonstrable antibodies to *C. burnetii*, antibodies were present in 12 of 30 goats tested. Inasmuch as the cattle herd is essentially a closed one, and is serologically negative, suspicion at present is centered on the goats, not only because of the high percentage with antibodies, but also because several acute illnesses, one quite severe, occurred in members of two families quartered on the ranch within several weeks after the goats were introduced there.

#### SUMMARY

Q fever has now been shown to occur in California, and the probability exists that more cases will be encountered. The presence of the disease requires that it be considered in the differential diagnosis of acute febrile illnesses as well as of the so-called viral pneumonias. Definitive diagnosis, however, rests on isolation of the rickettsia through inoculation of the patient's blood into guinea pigs, or by examination of paired serum specimens for the appearance, or rise in titer, of specific antibodies to *Coxiella burnetii*.

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## Primary Carcinoma of the Lung

### Diagnosis by Cytological Studies of Sputum and Bronchial Secretions

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A RECENT study of 200 cases of primary carcinoma of the lung that came to autopsy<sup>2,3</sup> revealed that the diagnosis usually had been made in the late stages of the disease or at autopsy. This late diagnosis of a disease which annually results in over 15,000 deaths in the United States is regrettable since thoracic surgeons are now able to remove the involved lung with "cure" in many cases if the diagnosis is established early. Consequently, attention should be centered on the early diagnosis of this disease.

The most important single factor in the diagnosis is that the physician must think of the possibility of bronchogenic carcinoma. Among the more common early respiratory symptoms are persistent cough, hemoptysis, pain in the chest and wheezing. Cough is relatively dry at first and is more productive later. Symptoms of this nature occurring in a patient, particularly in a male over 40 years of age, should immediately suggest the possibility of bronchogenic carcinoma. If the presence of this disease is suspected a thorough course of investigation should be carried out. This should include the taking of a careful history, physical examination, complete roentgenological study of the chest, and bronchoscopy. Lipiodol studies may be helpful. Often exploratory thoracotomy is necessary to establish the diagnosis.

Attention has been focused recently on a simple method of suggesting, establishing or confirming the diagnosis of primary carcinoma of the lung. Inasmuch as primary carcinoma of the lung is considered bronchogenic and the malignant cells tend to exfoliate into the lumen of the bronchus, it is logical to attempt to find these free cells in the sputum or

bronchial secretions. It is the purpose of this paper to discuss some of the more important features of this diagnostic method.

#### HISTORY

The presence of neoplastic cells in the sputum of a patient with bronchogenic carcinoma was first reported by Hampeln in 1887.<sup>4</sup> Hampeln and other early workers prepared sputum for microscopic examination in dried smears or imbedded histological sections which were usually stained by simple methods. Unlike the earlier workers, Dudgeon and Wrigley in 1935 used wet films which they fixed in Schaudinn's fluid and stained with Meyer's hemalum and eosin.<sup>1</sup> In 1944 Wandall in Denmark reported finding neoplastic cells in the sputum by using a wet film technique and staining with hematoxylin and eosin.<sup>9</sup> Herbut and Clerf reported on the adaptation to the study of bronchial secretions of the Papanicolaou technique for studying vaginal cytology.<sup>5</sup> Numerous other reports have appeared in the English, Latin-American and Russian literature.

#### METHOD OF PREPARING SLIDES

Material must be carefully obtained and slides properly prepared in order to preserve the cytologic detail essential for the recognition of malignant cells and differentiation of them from the normal cellular flora of sputum or bronchial secretions. If sputum is to be examined the patient is instructed to raise secretions from the lower part of the respiratory tree. Smears should be made immediately to avoid loss of cellular detail by autolysis. If there is to be a period of time before slides are prepared and fixed, it is best to have the sputum expectorated into jars containing 10 cc. of the fixative solution. Sputum should

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be examined in a Petri dish against a dark background. Various suspicious components of the sputum such as tissue fragments or blood flecks are selected, using a magnifying glass if necessary, and are gently smeared over two-thirds of the slide. Pressure will cause distortion during this procedure. Thick smears are not suitable for the study of cytologic detail. It is important to immerse the smears in the fixative solution while they are still wet. This fixative solution consists of equal parts of ether and 95 per cent ethyl alcohol. A paper clip attached to alternate slides will separate the smears.

Bronchial secretions obtained at bronchoscopy are treated in the same manner. Secretions should be obtained from suspicious areas of the bronchial tree for preparation of slides. If secretions are very scant all material should be saved.

We have found that after fixation for a two-hour period slides may be removed from the solution and permitted to stand, protected from dust, for at least seven days before staining. This permits mailing of slides to laboratories where trained personnel can examine the smears.

Smears are stained by the Papanicolaou technique. This method has been described in detail in the monograph of Papanicolaou and Traut on the diagnosis of uterine cancer by the vaginal smear.<sup>8</sup> It is not necessary with this technique to control the nuclear stain with microscopic observation as it is with hematoxylin and eosin.

#### CYTOLGY OF SPUTUM AND BRONCHIAL SECRETIONS

*Nonmalignant components.* The nonmalignant components of sputum and bronchial secretions are epithelial cells, cells from the blood and cells from the reticulo-endothelial system. Epithelial cells include ciliated columnar cells from the trachea and bronchi. Squamous cells originate in the mouth, pharynx and occasionally, in areas of metaplasia in the lower part of the respiratory tree. Blood elements which may be observed include erythrocytes, polymorphonuclear leukocytes, lymphocytes, monocytes and, occasionally, megakaryocytes. The reticulo-endothelial system contributes macrophages (histiocytes) and giant cells. Macrophages may exhibit marked pleomorphism. They may be mistaken for malignant cells, particularly when they do not contain phagocytized particles. A careful and thorough study of sputum from patients suffering from various types of nonmalignant respiratory disease is a necessary prerequisite to study of smears for neoplastic cells.

*Malignant components.* Neoplastic cells found in the sputum and bronchial secretions may be classified as differentiated and undifferentiated. Differentiated neoplasms in the lung include squamous cell (epidermoid) carcinomas and adenocarcinomas. It is not always possible to assign one malignant cell to the appropriate classification when it is encountered alone. When groups of malignant cells are seen it may be possible to classify them. The average malignant cell usually is large but it may not be, particularly if it is exfoliated from anaplastic carcinomas.

The nuclear-cytoplasmic ratio is usually large and at times the nucleus may appear to be naked. The nuclei may attain excessive size. They can vary in shape, position and size, and one cell may have more than one nucleus. This variability is particularly noted when various malignant cells are compared. The chromatin is usually arranged in irregular fragments or in a coarse meshwork. Mitotic figures may be observed. Nucleoli vary in size, shape and number from one cell to another. Groups of malignant cells may be crowded together in a manner not seen in macrophages or other normal cellular components. Phagocytosis is rarely exhibited by malignant cells.

#### RESULTS OF CYTOLOGIC STUDIES

Wandall reported finding neoplastic cells in the sputum of 84 of 100 cases of bronchogenic carcinoma. Herbut and Clerf preferred to work with secretions aspirated at bronchoscopy because the specimen was less diluted with secretions from upper portions of the bronchial tree. They reported malignant cells in 46 of 57 (89 per cent) cases of proven bronchogenic carcinoma. Woolner and McDonald<sup>10</sup> reported that they were able to demonstrate neoplastic cells in 70 cases, but it is not clear in how many of their cases the diagnosis was substantiated by tissue studies nor in what percentage of proved bronchogenic carcinoma the smears were positive.

We have used this diagnostic method for 15 months, and cytologic study of 1,512 specimens from 414 patients suspected of having "carcinoma of the lung" has been carried out. Positive or suspicious cells were found in 69 cases. Pathologic confirmation of the diagnosis of carcinoma of the lung has been established in 56 cases. In 46 (82 per cent) of these 56 cases, cytologic examination revealed or suggested the presence of bronchogenic carcinoma. Sputum smears were obtained in 52 cases of proved malignant disease; in 43 (82 per cent) of these cells were found which indicated or suggested the diagnosis of carcinoma of the lung.

As diagnostic criteria were developed and perfected our efficiency improved. As with any technique many of the early mistakes were found to be avoidable. We feel that diagnostic efficiency will be increased as a result of additional experience in evaluating the appearance of malignant, as well as the normal, components of the sputum.

#### REPORT OF THREE CASES

Three cases in which malignant cells were demonstrated in the sputum and the diagnosis was later confirmed by tissue examinations, are presented.

**CASE 1.**—A white man 67 years old was hospitalized on July 31, 1947. He complained of malaise, loss of weight, difficulty with breathing and a productive cough of four months' duration. Roentgenographic examination revealed an infiltrative process along the right cardiac border (Figure 1). On August 5, examination of a specimen of sputum revealed cells which suggested the presence of malignancy (Figure 2). At bronchoscopy a polypoid tumor was found which seemed to originate from the posterior wall of the right main stem bronchus, 1 cm. below the carina. Results of study of a

biopsy specimen were negative but bronchial smears revealed malignant cells. Biopsy was repeated and the tissue revealed epidermoid carcinoma (Figure 3).

CASE 2.—A 65-year-old white man was hospitalized on December 30, 1946. He had had hemoptysis, cough, had been

raising mucus for two months and had lost weight during that time. The sputum was found to contain tubercle bacilli. On roentgenologic examination evidence of chronic bilateral inflammatory disease and a circumscribed density in the right upper lung field (Figure 4) were observed. Bronchoscopy on January 7 did not reveal abnormal findings. A

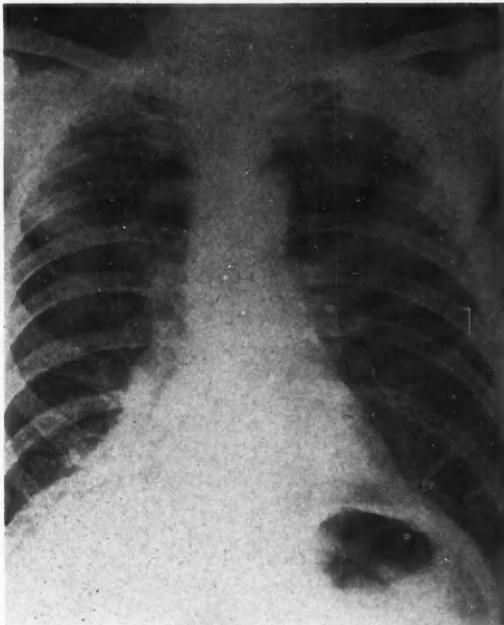


Figure 1

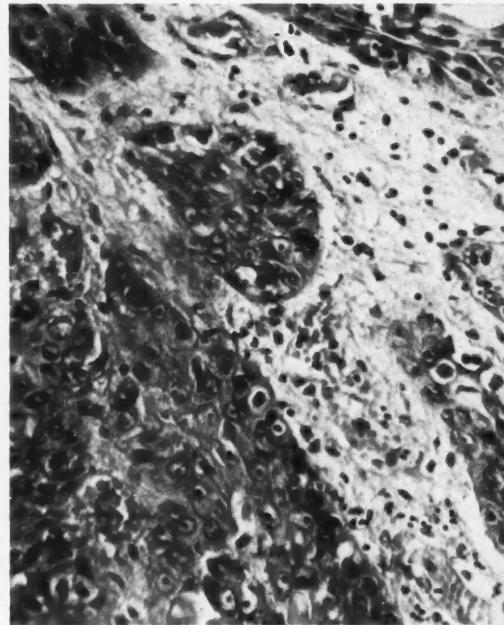


Figure 3

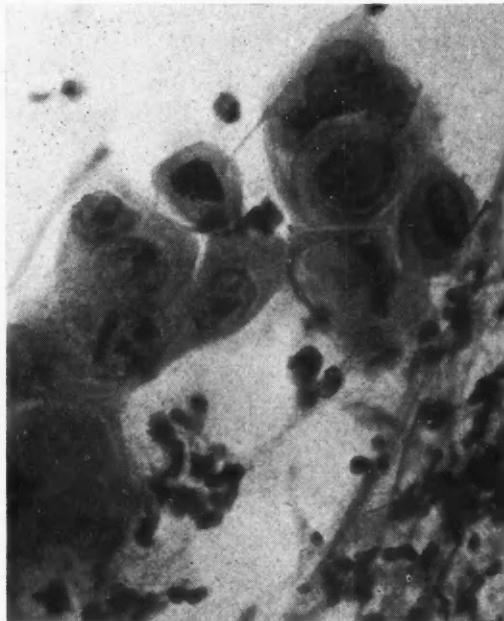


Figure 2

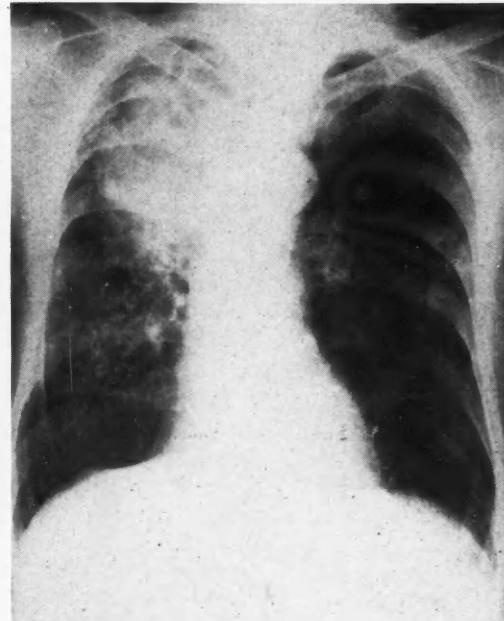


Figure 4

bronchogram revealed the presence of an obstructive lesion of the right upper lobe bronchus. In July sputum was submitted for cytologic study and was found to contain many malignant cells (Figure 5). The patient subsequently died and at autopsy an adenocarcinoma and coexistent pulmonary tuberculosis were found (Figure 6).

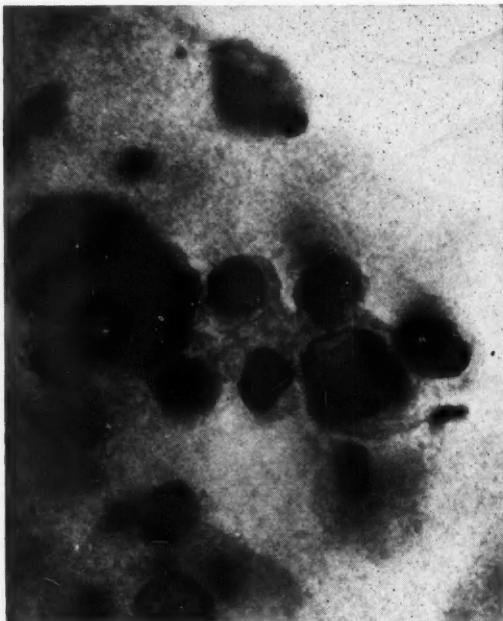


Figure 5

CASE 3.—A 61-year-old white male was first seen by one of the authors in May, 1947. He had had pleuritic pain, cough productive of a small amount of blood on several occasions and night sweats for eight months, and he had lost weight. A roentgenogram revealed evidence of atelectasis of the lingular segment of the left upper lobe (Figure 7). On May 20, examination of a sputum specimen revealed malignant cells (Figure 8). A week later bronchoscopy revealed a mass in the left upper lobe and a rigid, deformed left main stem bronchus. Left pneumonectomy was per-

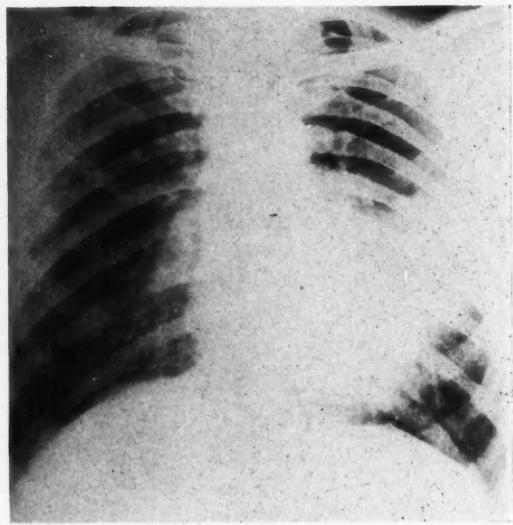


Figure 7

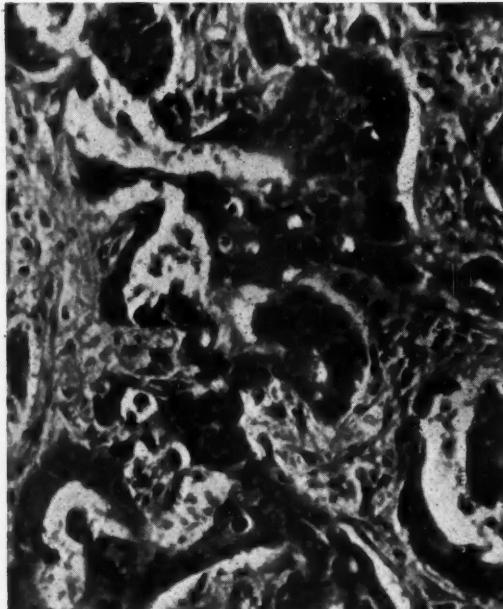


Figure 6

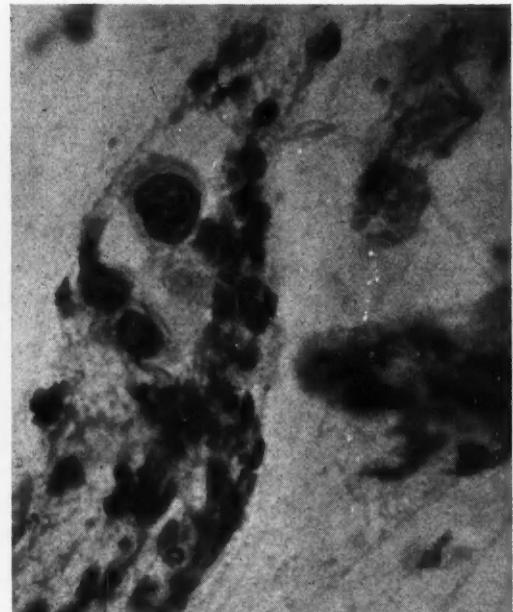


Figure 8

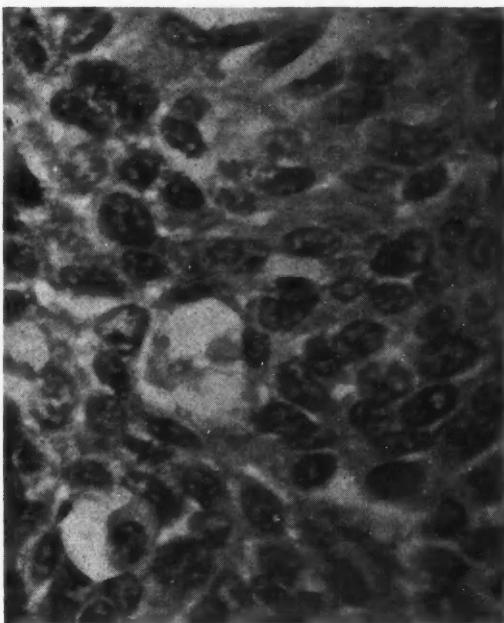


Figure 9

formed. Examination of the tissue revealed that a primary epidermoid carcinoma of the lung (Figure 9) was present.

#### COMMENT

The detection of malignant cells in the sputum is a relatively simple procedure. Malignant cells can be demonstrated in the sputum or bronchial secretions in at least 80 per cent of all patients with primary carcinoma of the lung. This figure compares most favorably with the results obtained by bronchoscopy with biopsy; it is considerably higher than the figures reported in many series of cases in which bronchoscopy and biopsy are used.<sup>6</sup> Skilled bronchoscopists are available only in certain medical centers. On the other hand, sputum can be prepared for study in any city or town and submitted to experienced observers. Bronchoscopy must be carried out, however, to evaluate the location and operability of the tumor.

Most bronchogenic carcinoma arise in the major bronchi and a considerable period may elapse before they reveal themselves on the roentgenogram by producing stenosis or a recognizable mass. During that time the tumor may metastasize. It may be possible to demonstrate exfoliated malignant cells in the sputum before roentgenologic changes appear. When the tumor develops in the peripheral portion of the

lung it may produce roentgenographic changes early but the nature of these changes is difficult to evaluate. Prompt and thorough examination of the sputum, if indicated, and confirmation of the diagnosis of malignancy by cytologic study will lead to earlier and more frequent surgical treatment. This should enhance the chances for a favorable result from surgical resection.

If cancer is present, inability to demonstrate cancer cells in the sputum is frequently due to failure to examine a sufficient number of slides from an adequate series of specimens. It must be emphasized that failure to find malignant cells on smears made from a single specimen does not rule out the diagnosis of carcinoma any more than does a single negative result of examination of the sputum for tubercle bacilli exclude the possibility of tuberculosis. In our series whenever possible five or six slides made from each of five specimens were examined. At times it was found necessary to obtain more than five specimens before malignant cells were demonstrated.

#### SUMMARY

Exfoliated neoplastic cells in the sputum of patients with primary carcinoma of the lung can be identified in an appreciable percentage of cases after diligent examination. The utilization of the Papanicolaou technique for the examination of sputum and bronchial secretions is outlined. Three cases in which this procedure was of value in suggesting, establishing or confirming the diagnosis of bronchogenic carcinoma are reported.

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## Practical Principles of Psychotherapy for the Non-Psychiatrically Trained Physician

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### INTRODUCTION

THIS paper is motivated by the average physician's perplexity which arises when he is confronted with the "management" of patients who present neuroses or psychological problems. The experiences of the last war have focused attention on the importance of psychiatry to all branches of medicine, causing more interest on the part of physicians and greater receptivity on the part of the laity. The term psychosomatic medicine has given new dignity to the problems involved and more and more energies of the clinician are being devoted to the psyche in illnesses previously considered entirely physical or somatic. A large percentage (variously estimated at from 30 to 60 per cent) of patients seen in medical practice are affected with neuroses. There are not enough psychiatrists to meet this problem and it is not necessarily desirable that there should be. The specialist, however, should be of aid in delineating to the practitioner what procedures he can logically and most effectively utilize. All too frequently, because of conflicting schools of thought, the psychiatrist's advice has created confusion rather than clarity.

The recommended approach should be as largely devoid of the theoretical and controversial as possible, and the simple, common sense, and factual should be given first trial. The following recommendations are culled from experiences in outpatient department teaching of senior medical school students and the directing of a psychiatric clinic where volunteer psychiatrists of different disciplines (eclectics, psychobiologists, and psychoanalysts) treat ambulatory patients.

A word must be said as to the objectives of psychotherapy. As usually presented these are too formidable to be attained by the practitioner. Psychotherapy has become too much identified with the claims of classical psychoanalysis where therapy is intensive, prolonged and complicated by a hierarchy of theory—and correspondingly very expensive. This is frequently based on the erroneous premise that the individual, to get well, must undergo a complete character transformation or at least detailed and tedious exploration of past life experiences. Space does not permit a full discussion of all the principles involved. Suffice to say that fortunately the organism contains many forces operating toward maintaining good mental as well as physical health and all that is necessary in many instances is to give the organism a little boost over a difficulty so that the individual can effect the rest of the recovery himself. It is well to bear in mind that many psychogenic dis-

orders are righted spontaneously without the aid of external intervention, at least without that based on recognizable scientific principles. Hence, in considering psychotherapy the following series of objectives arranged in order of increasing complexity may be entertained.

1. The establishment of insight that the symptoms are of psychogenic origin.
2. The removal of symptoms by relieving tensions in precipitating situational conflicts.
3. Attempts to resolve long-standing neurotic patterns.
4. Uncovering and removal of repression of traumatic early experiences where these are present and significantly related to the causation of the neurosis.

These objectives pass from the simple to the complex and perhaps only the first two are within the realm of the general practitioner, although possibly (and exceptionally) even the third. Surely the first, namely the ability to develop insight in the patient as to the emotional factors of his illness, is a most important objective and is often not difficult to attain. The physician, if he does nothing more for his patient, will serve a very useful purpose in shunting him from his search for more and more examinations, laboratory procedures and even unnecessary operations to attempt to ascertain the truly significant emotional tensions involved. Often this type of orientation, plus a prescription of the mental hygiene procedures which follow, is all that may be necessary to handle the patient's problem and at the same time serve an infinitely great value in preventing more serious protracted neurosis.

The attempt to relieve tensions and acute conflicts must most logically follow the uncovering of problems in the patient's total life situation, and often this can best be effected after the personal history has been taken. The interview treatment of chronic neurotic patterns is probably too complicated for the non-psychiatrically trained physician and belongs in the sphere of the specialist.

### APPLICATION OF MENTAL HYGIENE REGIMEN

The great majority of psychoneurotics do not live up to the recognized standards of simple mental hygiene in their every-day life. This is readily appreciated by the patient. Recommendations to correct the deficiencies are usually easy to follow and involve a minimum of theorizing. Correspondingly, results are soon apparent. There will be some individuals, however, whose deep-seated conflicts may make it impossible for them to carry out these recommendations.

No attempt is made to cover the whole area, but instead attention is here given to a number of items which the author has found to be of practical importance.

1. *Sleep.* Because of the prevalence of the symptom of insomnia in the face of emotional problems, this item is given prominence in our discussion. Emphasis is placed on insisting that the patient spend no more than eight hours in bed. Failure to secure adequate rest the first night in bed creates physiologic demand for sleep the following night. The success following the actual enforcement of this prescription is striking in view of its simplicity. Its merit in preference to the common practice of using hypnotic drugs needs no further comment.

2. *Morning Shower.* Because of the prevalence of inertia, fatigue and ill feeling in the first hours after awakening, the necessity of tonic stimulation to the nervous system is generally appreciated. A hot or warm shower followed by an abrupt transition to cool or cold temperatures in the final one or two minutes has proven very satisfactory. Patients frequently comment upon its favorable effect.

3. *Diet.* Owing to the elimination one foodstuff after another as a suspected cause of gastro-intestinal symptoms, many a neurotic patient is on a deficiency diet. A normal diet high in protein, minerals and vitamins is prescribed. This gives the physician an opportunity to explain the mechanism whereby emotional tensions interfere with normal gastro-intestinal processes, thereby relieving the patient from the stigma that his symptoms are imaginary. The explanation of the production of visceral symptoms via the autonomic nervous system resulting from psychological stresses lays the basis for further psychological discussions. Emphasis is also placed on such hygienic aspects as avoiding hurry and emotional tensions at meal times and the encouragement of eating in company.

4. *Play.* Play and social activity are two of the chief forms of rest to the tense nervous system and the proper application of both these activities will often give the patient at least temporary respite from his emotional problems. Sports out of doors are preferred. Tennis and golf are among the best because they preclude the possibility of preoccupation. Play without the play spirit, "perfectionist striving," is cautioned against. Other forms of play instead of sports may be necessary for those unable to engage in such active exertion. Here the physician must rely upon his common sense and the ability of the patient to adapt the principles to his own needs.

5. *Social Activity.* Stress is placed on the necessity of planning one's recreation. Patients frequently require education and encouragement in the process of socialization and in replacing or adding to obligatory social activity (e.g. relatives, business associates) and thus attaining a social life more satisfying to their own needs. A minimum of two sessions of play and two sessions of social activity per week is desirable frequency for the average well person.

In the presence of symptoms and in the absence of a full time job, the patient would do well to have two such "rest periods" for the nervous system each day.

Obviously these items do not cover the entire field of mental hygiene. These are features which can be universally applied. In addition many individual problems calling for recommendation will be apparent, as to work, strivings, etc. The recommendations are simple to comprehend, the patient's progress with them is easy to follow and may be the basis for discussion on successive interviews.

#### COMMON SENSE APPROACH TO LIFE MALADAPTATIONS

Basic in the application of modern psychiatric principles to therapy is the recognition that nervous tensions and symptoms are engendered from conflicts resulting from frustration and blocking of urges, desires, and ambitions. The next therapeutic approach of increasing complexity is therefore evaluation of the patient's adjustment to life's major situations. This calls for a life history of the patient referable to early family relationships, schooling, occupational history, sexual, marital and parental experiences, life ambitions, philosophies and religious attitudes. It is essential that every physician become familiar with this history-taking as a part of his medical armamentarium. Such a history form is presented in Chart 1.

Obviously if the patient spontaneously presents the major emotional problem then formal history-taking may be unnecessary. There are even some who believe that history-taking interferes with the patient's recital of crucial feeling-laden material and misdirects the individual from assuming an active participation in the solution of his problem, placing it in the lap of the doctor. It has been our experience, however, in short-term therapy, that the omissions in the absence of such a history, have often been serious and that one can learn to handle the situation without the shortcomings mentioned.

From a record of the contributing and interfering factors in the major life adjustments, the physician is in a position to utilize logic as well as specialized knowledge in the discussion of these problems with his patient. This does not mean that the physician need take an active role in deciding or settling issues for the patient. More frequently a passive, non-directive<sup>1</sup> attitude permits the patient's feelings to come to the surface, with emotional releases which are more important in getting relief of symptoms and a crystallization of his adjustment than a purely intellectual solution of the problem. Indeed, discussion and resolution of the conflict involved may give the patient complete relief, particularly in the so-called situational neuroses. A more formal knowledge of the principles of psychotherapy, however, may be needed if clinical improvement does not occur without its application.

#### OUTLINE OF PSYCHOTHERAPEUTIC PROCEDURE

An outline of psychotherapeutic procedures, including those of most intricate psychiatric practice, may have merit for the general practitioner since it

**CHART I**  
**PERSONAL HISTORY**

*Birth and Early Development:*

Mother's health during pregnancy; term; order of birth; hours of labor; presentation; instrumental delivery; rupture of bag of waters; birth cyanosis; birth weight; excessive crying after birth or difficulty in feeding; jaundice neonatorum. Age of teething, walking, talking.

Neuropathic stigmata; "nervous child," thumb sucking, bed wetting, nail biting, sleep walking, nightmares, tantrums, special fears.

*Family Relationships and Environment:*

Happy childhood? Adequate play life? Obedient? Sensitivities, geniality of environment.

Parents: Nervous manifestations, state of health, occupation, degree of skill and efficiency, religious attitude, relation to patient and to other children, social attitude, education and cultural background.

Siblings: Age, relationship, ties, jealousies, rivalries and comparisons.

*Educational Adjustment:*

Extent (number of schools also); efficiency and attitude.

Adjustment to teachers, students and objectives.

Extramural activities.

*Occupational Adjustment:*

Positions; duration and remuneration in each; reason for change; satisfaction.

*Sexual Adjustment:*

Pre-adolescent: Awareness; state of knowledge; experiences; attitude.

Adolescent: Age at first date; interest in opposite sex; frequency of social intercourse; attitude toward kissing and petting; "crushes" (overt and silent); masturbation; sexual preoccupation; sexual intercourse (friends, prostitutes, frequency, efficiency).

Adult: Marital, pre- or extra-marital sex relations; sex techniques and practices, adequacy, orgasm, contraceptive practices; compatibilities in marriage, physical, financial, cultural, ethical, parental and recreational. Separations, divorces, conflicts. Parental experiences.

*Ideals:*

Ideals, religion, philosophies, objectives and frustrations, political and social attitudes.

*Hobbies, Recreations and Daily Routine:*

Hobbies.

Recreations; out of door sports, play (cards, etc.) dancing, social activity, concerts.

*Personality Traits:*

Serious-minded, worrisome, sensitive, cry easily, harbor a grudge, suspicious, jealous, curious, envious, superstitious, seclusive, day dream, introvert.

Sad or happy, cyclothymic, irritable temperament, mix well, many friends, life of party, tell jokes.

Meticulousness as to belongings, person and work, punctual, resent waiting, opinionated, rigid, prudish, stubborn, generous or selfish, hypochondriacal, honest, conscientious, resent criticism, take a joke, pedantic.

*Summary:*

In terms of adjustment to each of major life situations.

calls attention to principles under which he can apply measures which common sense dictates in the absence of specialized knowledge and expert technique. It may aid in calling attention to possibilities he would otherwise overlook.

**1. Rapport.** The first step in all psychotherapeutic procedure is the establishment of rapport, or confidence. A careful examination and a kindly, sympathetic attitude towards the patient's problem often contribute most in this direction. Its effect in all medical therapy is great, even when not consciously appreciated. In its absence, psychotherapy can be little utilized, if at all.

**2. Ventilation or catharsis.** The beneficial results of permitting the patient to tell his story in his own way is universally recognized. There is a lessening of one's anxieties by "talking out" one's problems. Frequently this is very apparent to the patient. He will say, "Doctor, you have not done anything for me yet, but I feel much better. Just talking to you has helped me a great deal." This principle is recognized as the basis of many non-medical procedures of psychotherapeutic value. The value of confessional and the efforts of the Oxford movement are largely traceable to this source.

The patient should be permitted and encouraged to do most of the talking. All too frequently there is the tendency for the physician to talk too much so that the material discussed is influenced by the doctor's preconceived ideas. One must avoid moralizing. The patient often has sufficient difficulty in talking of intimate life problems, without needing to face the possibility of disapproval by the therapist. Ours is not to pass judgment. We are interested in symptoms, not in sin.<sup>2</sup> Hence one must be not only a sympathetic listener but also a skillful listener.

Frequently crystallization of an amorphous, apparently insoluble conflict is accomplished in this manner and light shed where previously there had been dark uncertainty and fear.

**3. Desensitization.** In regard to many life problems the patient has repressions with pent-up emotions. Situations of this type have been referred to as complexes. Ventilation or catharsis may have helped only a little. It may require numerous discussions from many different approaches before the repressed experiences are uncovered with concomitant release of these pent-up emotions so that they are brought to the surface and dissipated. At times a precipitous, overdiligent attack on problems of great sensitivity make progress difficult since the patient is in no position to tolerate so painful an experience. He must be slowly eased into it.

Not infrequently the complex or emotional stresses are not apparent on simple history-taking. The physician may see his patient a number of times before essential material comes to light. Sometimes the information is willfully withheld or the patient may be unaware of the full significance of the material not divulged. A tendency for the patient to be embarrassed about, or to prefer not to discuss certain situations, or to belittle their significance, must be noted

as indicative of subjects to be cautiously but definitely discussed again. It is important to be on the lookout for underlying feeling, e.g. anxieties, guilt feelings, insecurities and aggressive reactions, instead of concentrating too fully on the intellectual content of the patient's story, since these frequently lead to the crux of the situation.

Because motivations in behavior are not always or even usually apparent, attempts to elicit material that the patient is not consciously aware of as being significant, are essential. It is in regard to the uncovering of these unconscious motivations, which is necessary for desensitization, that the many separate schools of psychiatry differ.

Special procedures for bringing such buried emotionally burdened conflicts to the surface include association tests, sodium amyral and pentothal interviews, hypnosis, the free association method of psycho-analysis and interpretations of dreams. Obviously, these more specialized uncovering techniques involve the most controversial and theoretical aspects of psychiatry and are for the specialist.

**4. Suggestion.** Suggestion, which includes assurance, encouragement, and persuasion, are psychotherapeutic procedures, frequently employed by all physicians. The role of prescriptions, placebos, physiotherapy, "bedside manner," and injections (some of which are often of questionable justification, in and of themselves) as suggestive measures is well recognized. The most intensive form of suggestion is hypnosis. Its use should be reserved for special situations by the specialist.

**5. Education.** Although a "non-directive" attitude in psychotherapy is considered most favored in most techniques, yet there is no psychotherapy in which the physician's thinking and attitudes does not play a role in influencing the patient. Obviously the degree to which this takes place in different techniques varies. It is doubtful whether one ever gets to the bottom of all one's personal difficulties in psychotherapy. It is important to recognize that in each individual there are resources operating toward wholesome growth and normality. In many instances, as stated previously, all the patient needs is to be given a boost over a particularly difficult situation and his natural resources do the rest of the job.

Discussion of inadequate adjustment to life situations, as revealed by the life history of the patient, leads to enlightenment in regard to life values, modes of living and overcoming insecurities, inadequacies and other maladaptations. Under the heading of education may also be listed those recommendations previously listed under "mental hygiene regimen." A common-sense appraisal of pertinent life situations involved is often invaluable. The physician may often

be called upon for factual knowledge, particularly as to sexual matters. The development of insight, which is contributed to by many of the psychotherapeutic principles discussed, is also a matter of education and in this respect the understanding of the psychogenic origin of the illness is of paramount importance.

**6. Rehabilitation.** What can be done for the psychoneurotic patient in attempting to place him back in the ranks of the happy and efficiently adjusted individuals? First and foremost, the patient needs an adequate understanding and sympathy of his illness on the part of his family and friends. This interpretation should be the role of the attending physician. Help in the choice of occupation, securing special training, obtaining a position, and material aid for the patient and members of his family, and many other services which are available through community agencies and friends may be necessary in the rehabilitation.

When the physician has utilized these procedures, exhausting his fund of knowledge and common-sense approach to the apparent problems, and the patient is still in need of help, then the case becomes one for the psychiatrist. The program outlined, therefore, has merit not only in pointing out what direction the efforts of physicians who are not informed in the theory of psychiatric practice can best take, but also in setting up the indications for the specialist's care—indications not based solely on the ability of the patient to pay, as is so frequently the case.

The recommended procedures call for the application of principles from the simple to the complex. First there is the attempt to get the patient to live according to the best tenets of mental hygiene, a procedure designed to restore or develop a reserve of nervous stability. Then the physician approaches the life history of his patient to ascertain the adequacy of his adjustment to life's major situations and applies the principles of psychotherapy as his insight and untutored common sense dictate to him. Failing then, he looks for more expert aid.

It is to be lamented that the specialist so frequently, in his zeal and confidence in controversial techniques, neglects to obtain the benefits to be derived from the simpler measures. It is hoped that the recommendations made offer a practical outline for the non-specialist's approach to the psychoneuroses and psychosomatic problems of every-day medicine.

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## Pancreatic Lithiasis and Calcification

### A Study of 22 Cases in a Series of 35,000 Necropsies

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THE presence of calculi within the ducts of the pancreas presents problems in pathogenesis, diagnosis and treatment which are difficult to solve. During the past decade, however, much progress has been made toward that end. In this paper we shall briefly review the problem and some of the more recent contributions to our knowledge, as well as report 22 additional instances of lithiasis or diffuse calcification of the pancreas.

As pancreatic calculi arise from the juice within the ducts, the normal chemical and physiological mechanisms involved in its elaboration are of basic importance. Pancreatic juice is secreted chiefly following meals, but continuous secretion in the fasting state in man is indicated by the experiments of Agren and Lagerlof<sup>1</sup> and Frish and Welin<sup>12</sup> to be about 12 cc. per 20 minutes. Difficulties in arriving at the true figures include the exclusion of hydrochloric acid from the duodenum and the possibility of bile entering the duodenum and stimulating pancreatic secretion during this experiment. The total 24 hour secretion of the pancreas in man may be much higher than the usually accepted figure of 700 cc., according to Miller and Wiper.<sup>21</sup> They studied three patients with external pancreatic fistulae. One of these produced as much as 1,770 cc. in one day. As his digestion was not disturbed and the stools were normal as to fat content, sufficient amounts of juice were probably entering the duodenum for intestinal digestion. These authors, therefore, believed the total daily secretion in man might reach 2,400 cc. Harms<sup>16</sup> found the pressure within the ducts of the pancreas during the height of secretion to be considerably higher than that in the common bile duct; only during fasting was it lower.

The quality of the pancreatic juice differs greatly, depending upon the stimulating agent. With vagal or pilocarpine stimulation the juice is small in quantity and high in enzyme activity. With secretin stimulation the juice is much greater in quantity, more alkaline and poor in enzymes. Komarov, Langstroth and McRae<sup>18</sup> in 1939 confirmed and further elaborated the work of Ball<sup>4</sup> in 1930 and that of Gamble and McIver<sup>13</sup> in 1928 regarding, first, the relationship of chloride and bicarbonate fractions to the degree of alkalinity and, secondly, the similarity of the inorganic constituents of the juice to the level of the same ions in the blood serum. In the juice of both dogs and man the inorganic ions are chiefly sodium, bicarbonate and chloride. The other ions—potassium, calcium, magnesium and phosphate—are present in much smaller quantities. Injection of sodium

and potassium into the blood stream increases their content in the blood serum and pancreatic juice to the same degree. Thus it is assumed that the pancreatic acini are freely permeable to these ions. Calcium, magnesium and phosphate are secreted with much more difficulty. Ball also demonstrated in dogs that the blood serum and pancreatic juice had identical osmotic pressures. The pH of the juice increases with secretory activity. This is due to an increase in the bicarbonate fraction and a concomitant decrease in the chloride. However, the sum of the two remains constant. Ball observed during the height of secretory activity a pH of 8.24. He calculated that 8.3 was the maximum pH the pancreatic juice could reach by assuming a free  $\text{CO}_2$  concentration of 1 millimol and a maximum bicarbonate of 150 millimols.

Most pancreatic calculi are composed chiefly of calcium carbonate and small quantities of tribasic calcium phosphate. Magnesium carbonate and calcium oxalate have occasionally been observed. Stones have also been classified into inorganic and organic types, the latter containing fat, fatty acids, carbon, cholesterol and albumin, bound together with calcium salts.<sup>7</sup> It has been assumed by many that because of the low concentration (1 to 1.7 millimols) of calcium in the pancreatic juice the formation of calcium carbonate calculi is difficult to explain and that additional factors such as inflammation with outpouring of more calcium might be necessary. On theoretical grounds this may be disputed if one takes into consideration the fact that the pH in the human pancreatic juice goes as high as 8 and the bicarbonate as high as 127 millimols.<sup>3</sup> Under these conditions the solution, even with 1 millimol of calcium present, is supersaturated.\*

Pancreatic lithiasis may be symptomless or there may be a long history of upper abdominal complaints. The occurrence of solitary stones without symptoms is not unusual and their origin is only conjectural. Comfort, Gambill and Baggenstoss<sup>10</sup> at the Mayo Clinic in 1946 made an outstanding contribution in their study of 29 cases of primary "chronic relapsing pancreatitis." The disease is characterized by repeated attacks of upper abdominal pain, elevated serum amylase and lipase values and often temporary derangement of both the external and islet cell secretions. With repeated attacks the latter changes may become permanent and diabetes mellitus, steatorrhea and creatorrhea may be present. Stones or diffuse calcification was diagnosed in 14 of the 29 cases. Comfort and his co-workers divided these 29 patients into seven clinicopathological

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\*Detailed calculations regarding the physical chemistry involved will be published in the future in collaboration with John W. Mehl, Ph.D.

groups, depending upon the presence of pain alone or various combinations of pain followed by one or more of the major complications: diabetes mellitus, steatorrhea or lithiasis. They believed the stones were secondary to the pancreatitis and observed the formation of calculi, while patients were under their care, within one to fourteen years after the onset of pancreatitis. This disease is of great importance because a diagnosis can so often be made with great certainty. The exact mechanism of stone formation in the ducts of a pancreas subject to repeated attacks of inflammation is not known. Obstruction, stasis, epithelial desquamation and inflammatory exudate may all play a part in instigating the process. Alcohol probably acts only in precipitating the pancreatitis by overstimulation. Jaleski<sup>17</sup>, noted that 45 per cent of the patients having pancreatic lithiasis reported in the literature were alcoholics. Recently Wechsler and Weimer<sup>26</sup> reported two younger individuals with pancreatic lithiasis whose abdominal symptoms began in childhood at the ages of eight and ten, and the calculi were diagnosed at the ages of 27 and 28. These patients were not alcoholics. It has been suggested that there is a possibility of calculi being a late complication of cystic fibrosis of the pancreas, a disease usually seen in the first two years of life.

The incidence of pancreatic lithiasis is low. In nearly all articles on the subject the total number reported in the literature is mentioned and brought up to date. The latest tabulation noted is that of Lionello, Ficarra and Ryan,<sup>19</sup> in which the total reported was 225. As the total number appears to be growing at a more rapid rate, its importance seems to be diminishing. The incidence in various autopsy series varies considerably. Pascucci<sup>22</sup> tabulated all those reported previous to 1944. There were 52 instances in a total of 117,031 routine necropsies, an incidence of 0.044 per cent.

Beling<sup>5</sup> in 1940 first made the suggestion that diffuse calcification of the pancreas be separated from the more common form of the disease in which there are only discrete intraductal calculi. He collected 12 instances from the literature and added one. He gives Allen<sup>2</sup> credit for the first reported case in 1903. Wirts and Snape<sup>27</sup> in 1947 collected 22 cases from the literature plus two of their own. The patients have minute calculi in the finer ducts and in the acini. The calcification is said not to involve the epithelium of the acini. Severe interlobular fibrosis and acinar atrophy are usually present. The larger ducts may be dilated and also contain minute calculi. The basis for separation of this group is that apparently the disease begins in the smaller ducts or acini and involves the entire gland, producing a stone-hard organ that can be distinguished by x-ray examination to have a separate pattern. From the clinical standpoint this group is closely similar to the larger one in which sizable calculi are in the ducts.

#### DIAGNOSIS

Many articles have dealt with the diagnosis of pancreatic calculi. It is agreed that a flat roentgenogram of the pancreatic area is of most importance. This should be made before any barium is present

in the digestive tract or gallbladder dye studies are attempted. If shadows are present in the pancreatic area, Beling<sup>6</sup> emphasizes the importance of lateral films in order to bring out their relationship to the spine. The pancreas lies 1 or 2 cm. in front of the spine, although the tail may be curved and on the same plane as the body of the vertebrae. Four types of calculi have been described by Gillies.<sup>14</sup> The differentiation of disseminated calcification from discrete calculi depends upon the demonstration of a diffuse, stippled calcification involving the head, body and tail.<sup>27</sup> In addition to roentgenologic evidence of calcification in the pancreas, studies of the external secretions are of importance. A notable step in this direction was made by Agren and Lagerlof.<sup>1</sup> They have introduced the use of a specially designed double-lumened tube, to be introduced into the stomach and duodenum, which aspirates both gastric and duodenal secretions at the same time. With secretin injection intravenously there is a prompt increase in the volume of the pancreatic juice and especially an increase in bicarbonate and enzymes. In both chronic pancreatitis and stone, marked reduction in volume, alkalinity and enzymes may be observed.<sup>9</sup> In recurrent attacks of pain associated with chronic pancreatic disease with or without calculi, studies of serum amylase and lipase<sup>10</sup> are most helpful. It is to be remembered that in long-standing obstruction by stone in the head of the pancreas coincidental with acinar atrophy the levels of amylase and lipase tend to decrease in recurrent attacks of pancreatitis. Other laboratory aids to diagnosis are well known and no particularly new developments have been noted. These include examination of the stools for fat and the percentages of neutral fat and fatty acids, tests for glycosuria and glucose tolerance tests.

#### REPORT OF CASES

There were 22 instances of pancreatic lithiasis and/or calcification among 35,000 consecutive autopsies performed between September 15, 1925, and August 19, 1947. They were evenly divided as to sex. The range of age was from 22 to 86 years, the mean age for the entire group being 53.4 years. The males were considerably older, the mean being 64.1 as against 43.6 for the females. Death was attributable directly to chronic pancreatitis and lithiasis in seven cases, and the disease was contributory in six. In the remaining nine instances the pancreatic disease was not a direct factor in the cause of death.

#### Clinical:

The symptoms and signs of the disease were not definitive. The following were noted at the time of the admission of the patients to the hospital.

SYMPTOMS	SIGNS
Upper abdominal pain.....10	Weight loss .....17
Weakness .....8	Hepatic enlargement .....11
Nausea and vomiting.....8	Jaundice .....5*
Constipation .....6	Edema .....1
Diabetes (thirst, polyuria or coma) .....6	Ascites .....1
Steatorrhea .....1	

\*In addition the examining doctors later noted icterus in nine additional cases, making a total of 14.

The chief presenting symptom was upper abdominal pain of some kind. No two patients complained of exactly the same symptoms. In some the pain was of a severe colicky nature, while in others it was a vague distress. Radiation of the pain was likewise of little assistance in making a diagnosis. Sometimes it would radiate to the right upper quadrant, other times through to the mid-portion of the back. The pain seldom resembled that of biliary colic. One of the patients had pain in both flanks and was thought to have an acute pyelonephritis. The pain of pancreatic lithiasis is often associated with nausea and vomiting, but the two do not necessarily go together.

The other symptoms and signs noted by the patients, such as weakness, loss of weight and constipation, are of no help in arriving at a correct diagnosis. Steatorrhea occurred but once in this series; other forms of diarrhea were absent. Diabetes mellitus occurred in seven instances, and in six instances it was the primary reason for the patient's entry to the hospital. In one patient the disease was latent, being diagnosed by the glucose tolerance test. Four patients did not complain of pain. One was known to have had diabetes for three years, which had been controlled by diet until two days previous to final entry into the hospital. Jaundice was an outstanding sign in 14 instances, although only five patients noticed the icterus. The diagnosis of chronic pancreatitis with lithiasis was not made clinically in any of the 22 cases. A specimen taken of the head of the pancreas in one patient operated upon for obstructive jaundice resulted in a report of chronic interstitial pancreatitis. At necropsy this was confirmed but the underlying cause was intraductal calculi.

There was a definite history of long use of alcohol in ten instances. In two the matter was questionable, and in ten cases there was no notation of intake of alcohol.

The histories of two of the patients are of particular interest. One of these had obstructive jaundice due to pressure on the common duct and the case was reported in detail at the Clinical-Pathological Conference of the California Medical Association on May 3, 1947, by Dr. John Tragerman (published in CALIFORNIA MEDICINE, 67:256-258, October, 1947). The second case is as follows:

#### CASE REPORT

A white male mechanic, age 45, first came to the outpatient department on May 3, 1934, complaining of "bloating of the abdomen," a condition that had existed for 18 years. This would often cause so much distress that nausea and vomiting would result, with subsequent relief. No true abdominal pain was associated. Soda gave no relief. The attacks would last from one to five days and would recur every six to twelve months. For one year the patient's appetite had been poor and he had lost 15 pounds in weight. He used alcohol, but the history does not state in what quantities. On May 9 barium study revealed an irregular, tender duodenal cap. A diagnosis of duodenal ulcer was made. The patient returned to the outpatient department in June and July of 1934 complaining only of severe upper abdominal pain. He entered the hospital on August 13, 1935, complaining of similar pain but refused treatment and was discharged. He reentered the hospital September 2, 1935, from another hospital in a mori-

bund condition and died a few hours later. At necropsy no evidence of a duodenal ulcer was identified. The cause of death was a solitary stone in the duct of Wirsung with a complicating acute pancreatitis.

This history illustrates the difficulty in differential diagnosis between pancreatic calculi and duodenal ulcer.

#### Pathology:

Study of specimens in this series revealed only the end stages of obstructive disease of the pancreatic duct and therefore tells us very little of the genesis of the calculi.

**Gross Pathology:** The descriptions of the pancreases in gross are of interest chiefly from the standpoint of the location of the calculi and their complications. In nine cases calculi were within 2.5 cm. of the ampulla Vater. In two of these cases the calculi had obstructed the common duct, apparently by pressure and edema, which resulted in jaundice in both patients and biliary cirrhosis in one. Of particular interest was a large ivory-like stone which obstructed the duct of Wirsung in the head of the pancreas, but there was little dilatation or change in the duct system behind the obstruction. This brings up a point which appears to have been omitted in most published discussions of pancreatic calculi; that is, whether or not the communicating duct of Santorini may carry the pancreatic secretions to the duodenum when the duct of Wirsung is blocked. In ten patients the calculi were in the body or tail, or were described as being widespread in the duct system but no definite location was given. There were three instances of diffuse calcification of the pancreas, so-called petrificans, without stones in the duct. Of the entire group of patients, 16 had multiple calculi or calcification, and in six there was a solitary stone within the duct. Seven had one or more cysts somewhere in the pancreas. Some of these were apparently dilatations of ducts and others were pseudocysts. The complications were what one would expect with obstruction of the duct: three had acute pancreatic necrosis; two, healing fat necrosis; in four there was evidence of purulent inflammation, with solitary abscesses having resulted in two of them.

**Microscopic Pathology:** The microscopic changes were of interest because of the variations in degree of dilatation of the duct and fibrosis of the pancreas. With apparently similar degrees of gross obstruction there was great variation in microscopic evidence of dilatation. This again emphasizes the possibility of some of the pancreatic juice escaping through the duct of Santorini. Regardless of the degree of dilatation of the duct, dilatation of the acini was minimal or even absent. Rich<sup>24</sup> has proven that with increased pressure within the ducts fluid easily escapes between the acinar cells into the peripancreatic tissue. Diffuse perilobular and intralobular fibrosis were common, but atrophy alone appeared to have occurred in some instances, leaving little evidence of chronic inflammation and fibrosis. In some of those patients with solitary calculi, dilatation and atrophy alone were observed. The question of what role

repeated attacks of pancreatitis have in the formation of fibrous tissue arises but cannot be solved from this material. Islets apparently are not always, as has been taught, spared until the last. One of the patients had diabetes mellitus without great acinar atrophy or evidence of steatorrhea.

*Associated Pathology:* There were 14 in whom the liver was fatty. Eleven of these had cirrhosis. In eight it was Laennec's type; in two it was biliary cirrhosis due to obstruction of the common duct by a stone in the duct of Wirsung; and in one the cirrhosis was of the fatty dietary type with no particular relationship to periportal spaces or central veins—a condition similar to that described by Chaikoff<sup>8</sup> in experimental dietary fatty cirrhosis of animals.

#### COMMENT

It seems strange that in such a large series as this not a single correct diagnosis was made antemortem in spite of the fact that many of the known symptoms of pancreatic calculi were present. Because pancreatic disease was not suspected, laboratory procedures useful in diagnosis were not performed. One patient had a roentgenogram of the pancreatic area which showed calcification but this was interpreted as an artifact. The incidence of the disease in this necropsy series, 0.062 per cent, is somewhat higher than the general average of 0.044 per cent reported by Pasucci.<sup>22</sup> Six of the 22 patients in our series were seen within the year preceding the preparation of this paper. All were chronic alcoholics. During the same period calculi was diagnosed in a patient on the wards and we were consulted about another case by one of our colleagues. Thus, having seen or known of eight instances of the disease in one year, we feel that it hardly belongs among the rare diseases. Taking into consideration the present consumption of alcohol and the number of chronic alcoholics in the population, an increase in incidence of pancreatic lithiasis might be expected. The incidence in this series is probably much too low, as often the pancreatic ducts were not dissected at autopsy. At present we are examining a series by postmortem roentgenograms to compare with Ludin's<sup>20</sup> series in Basel. Ludin carefully dissected all pancreases showing calcific roentgenographic shadows and found 28 stones in 542 pancreases, giving an incidence of 5.1 per cent.

The complications of lithiasis in this series are similar to those that have been reported. Among the local disturbances within the pancreas are atrophy, acute pancreatitis, abscesses and pseudocysts. Many of the stones were probably due to recurrent attacks of pancreatitis of the type described by Comfort.<sup>10</sup> In patients with symptomless solitary stones in whom no evidence of chronic inflammation was noted, other explanations for the formation of calculi should be considered. In four of the six patients with solitary calculi no symptoms attributable to the pancreas were elicited. It is possible, of course, that a minimal attack of pancreatitis forgotten by the patient could give rise to a stone.

Complications arising from pressure on contiguous structures, especially the common duct and duodenum, should be remembered. Additional pressure phenomena mentioned by Comfort<sup>10</sup> include pressure on the splenic vein and mesenteric vessels.

Perhaps the pathological physiological sequelae are the most interesting of all. These include diabetes mellitus, steatorrhea and fatty metamorphosis of the liver with or without cirrhosis. Increase in serum amylase and lipase may occur in the recurrent attacks of pancreatitis which often characterize the disease. Any of these, when present, constitute important leads to correct diagnosis. Flat films of the pancreatic region are now being requested on all patients entering the hospital in an acute attack of pancreatitis. It may be questionable from the economic standpoint whether the same procedure should be done on all diabetic persons. Seven, or 31.8 per cent, of the 22 patients in this series were diabetics. From the histological study of these it appears that occasionally the atrophy of the islets and acini proceeds at a parallel rate and the islets are not preserved until the last. In Comfort's<sup>10</sup> series of 29 there were four patients who had upper abdominal pain followed by diabetes and calcification, but there was no evidence of steatorrhea. Two causes for this may be mentioned: First, the calculi or calcification may involve primarily the body and tail, where most of the islets are present; even though there were great destruction here, the acinar tissue in the head of the pancreas might produce sufficient external secretion to prevent steatorrhea. Second, once islet tissue is partially destroyed, episodes of hyperglycemia may produce progressive damage to the islets alone, the effect being somewhat similar to that seen in experimental animals, both normal and partially depancreatized, in which prolonged intraperitoneal glucose-saline solution with hyperglycemia produced permanent damage to the islets.<sup>11</sup> The low incidence of steatorrhea (one in twenty-two) probably means that the stools were not examined carefully. The fatty change noted in the liver with or without cirrhosis was in every instance associated with chronic alcoholism.

The treatment of pancreatic lithiasis, when possible, is surgical.<sup>15, 25</sup> Discussion of this subject is beyond the scope of this paper. Haggard and Kirtley state that the results are good following the removal of stones. Early diagnosis and surgical treatment are emphasized by most authors. The importance of control of pain by sympathectomy and vagotomy has recently been introduced by Reinhoff and Baker.<sup>23</sup>

#### SUMMARY

1. Twenty-two instances of pancreatic calculi and/or calcification in a series of 35,000 necropsies are reported.
2. In 14 of these there were multiple calculi; in five they were solitary. Stones lodge most commonly in the first 3 cm. of the duct of Wirsung.
3. Calcinosis or diffuse calcification were present in four cases, and in three of these four there were no grossly detectable intraductal calculi.

4. Dilatation of the ducts, atrophy of the parenchyma, fibrosis and chronic inflammation occurred to a varying degree.

5. Fatal complications included acute pancreatitis, suppuration of the pancreas, and obstruction of the common bile duct.

6. Atrophy of acini and of islets may occasionally proceed at a more parallel rate than is usually recognized. Diabetes mellitus was present in seven patients in this series.

7. The signs and symptoms of the disease in this series were difficult of evaluation. Not a single case was diagnosed correctly.

8. The most important diagnostic aid is roentgenograms of the pancreas.

9. Alcoholism and recurrent pancreatitis resulting in fibrosis are common precursors of calculi and calcification. Ten in this series were chronic alcoholics.

10. Pain, weight loss, jaundice, and a palpable liver were the predominating clinical manifestations.

11. The disease may be symptomless.

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## A Pediatrician's Observations on Mental Hygiene

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IT would be both inappropriate and presumptuous for a pediatrician to attempt to inform an audience composed largely of psychiatrists on the general principles of mental hygiene as applied to children. It is, in fact, the psychiatrists who have provided much of the material on which our interest is based. The writer will simply try to present briefly what he thinks the present attitude of pediatricians on this subject is, and something of the why and how this attitude has been reached.

Many of us began our pediatric practice in happy ignorance of such things as conflicts and neuroses and long before the term "mental hygiene" was coined. Behavior, attitudes, and parent-child relationships had no more to do with clinical pediatrics than had astronomy. We thought we knew something of growth and development and physiology and pathology on the physical side and how to diagnose and treat the various physical defects, abnormalities, infections, and accidents. But it was indeed a shock to discover very quickly that pediatrics is not like that. When we took our first history, asked for the chief complaint, and were told, "This child, since the arrival of his little sister several weeks ago, has become sullen, disobedient, and destructive," then we realized that there had been gaps in our education. We suspected jealousy was the cause of the child's behavior, but had no idea what to do about it. We made feeble attempts to solve some of these problems, using a bizarre mixture of common sense, intuition, general experience, a few shreds of popular psychology, and a few guesses thrown in. Some of us developed an amazing aptitude for giving parents the wrong answers. Others adroitly evaded these questions, claiming a steadfast interest in strict clinical medicine, and looking hopefully for a case of pancreatic fibrosis or glycogen storage disease, meanwhile telling the mother of the child who wouldn't eat to "make him finish his plate and insist on the correct balance and the optimum number of calories."

But as time went on, and with the advancement of knowledge, the whole concept of the function and scope of pediatrics broadened. We became interested in the total welfare of the child and found ourselves, as Gesel says, "holding the most strategic position in the whole scheme of preventive and constructive medicine, since health protection begins with the beginning of life and growth." And we learned to think of the child as an indivisible unit in which physical well-being and mental welfare are reciprocal and inseparable. Then we began to see that our responsibility as pediatricians had expanded and that now we must help develop not only the best organic mech-

anism but the most satisfactory personality of which the child is intrinsically capable.

We began our search for sound scientific knowledge in the field of mental health, absorbing new studies in growth and development, groping our way through the strange and unfamiliar vernacular of the psychiatrists, listening to conferences at the child guidance clinics, picking up a morsel here and a bit there and trying to reject the unscientific overpopularized material—that of the cults and the superficial forms of pseudo-psychologic doctrine which have crowded the radio and the popular magazines. In his search for knowledge the writer even enticed a first rate psychiatric social worker into his office and over a period of years watched her uncanny skill in ferreting out the causes of unsatisfactory behavior and in improving parent-child relationships.\*

But at the risk of being accused of prejudice or of pride in profession, it must be recorded that we pediatricians are now learning more from each other than from any one else. That is to say, the studies and papers and books of pediatricians themselves are making the greatest contribution—perhaps because they are written from the pediatric point of view. The writings of such men as Aldrich and Spock provide the sort of sound and practical material with which one can build the tools and the method of his daily work.

We have practically abandoned the term "mental hygiene." Hygiene refers largely to the science of sanitation and one often thinks of it in connection with septic tanks, typhoid control, or such things as the prevention of dental caries. We prefer the term "mental health" and we think of a mentally healthy child as one who is growing in self-control and self-direction toward social ends—one who is developing an adequate personality, and one who is growing mentally and emotionally toward maturity. This growth takes place largely through his personal relationships and if his mental health is properly fostered he should, we think, eventually become a master in a typical pediatric office, not in terms of the well known symptoms demonstrated by the immature person, intellectually, emotionally, socially, and morally, which after all is what we are trying to accomplish.

We have learned that growing children thrive best

\*In contrast to these crude beginnings of the study of mental factors in child development, it is interesting to note the form these studies are taking now. Since this paper was written there has been held in Hershey, Pa., a most valuable conference on the mental health aspects of Pediatrics "for the exchange of information between two medical disciplines dealing with children—pediatrics and child psychiatry." It is both revealing and heartening to read the reports of this conference and to hear what is actually being done through the joint efforts of pediatricians, psychologists, and child psychiatrists in teaching, in practice, and in research at such medical centers as Cornell, Columbia, Minnesota, Harvard, Yale, Hopkins, Chicago, California, and Stanford.

mentally when they live in a climate of human attitudes and relationships which satisfies certain basic needs. And in order to prevent the stresses and strains which may lead to mental ill health we try to see that these basic needs are fulfilled. When we meet a problem in behavior (which we do almost every hour of every working day) we try to solve it in terms of unsatisfied needs.

In simplified form, the more important of these basic needs for the growing child we conceive to be as follows:

1. The need of security. We feel that the approval and affection which satisfy this need should be deserved, so that the child learns to acquire security through his own efforts.

2. The need to live in and face the actual reality of the world as it is and the people he has to live with, including himself. He must learn to control his impulses and fit them to social demands and he especially needs to develop the courage to face real facts and real situations without being hurt. He must stand up to life without evasion or retreat.

3. The need for activity leading to achievement which results in satisfaction. This includes the need for the recognition and friendship of contemporaries—the need for success.

4. The need for independence appropriate to age.

The pediatrician feels that when such basic needs as these are not met there is apt to be a problem expressed in terms of unhealthy attitudes and actions. The child is in distress emotionally and his conduct represents an effort to solve the problem. And when a child attempts to solve his own problem he often gets into difficulties with his behavior, which is poor mental health. And it is also true that as these needs are met the necessity of an imposed external discipline sinks into the background. When we can connect such symptoms as lying, truancy, enuresis, fears, temper tantrums, destructiveness, jealousy, or negativism with *insecurity*, for instance, we are already well on the road to treatment. Better still, by fostering security in the beginning, we are well on the road to prevention.

We think we have made considerable progress lately in fulfilling the need for independence appropriate to age. We have stopped regimenting infants into fixed schedules and rigid techniques. We have stopped "breaking" them into and out of habits at certain fixed and specific ages. We feel that the child has a right to pursue his own growth pattern, a right to be given food when he is hungry, and a right to refuse it if he isn't hungry. We are alert to help him take his next step ahead when he is ready to take it, but we respect his right to go along on his own individual developmental time-table.

It might be of interest to list a few of the most common problems in mental health which present them-fant or child, but in terms of certain attitudes often indulged in by the parents. We see the fearful and anxious mother, overpowered by her sense of respon-

sibility, constantly alarmed and in need of reassurance; the grimly determined and domineering mother who tries to force her child into habits, who creates issues and then imposes her authority in settling them, and who fights on down to the last bit of spinach; the over-protective and often possessive mother who tries to shield her child from all that may be unpleasant; the over-submissive mother who allows her child to make unreasonable demands and get them fulfilled; the frustrated mother who has read all the books but can't find the right answers for her child and has lost all spontaneity as well as her sense of humor; the nagging, scolding, threatening mother who expects adult behavior at the five-year level; the mother who wants to give her child what she herself lacked in her childhood; the mother who allows the grandmother to direct all operations because she herself has never become emancipated from maternal control; the mother who holds too tight a rein over her adolescent daughter; the mother who sees only the annoying faults but none of the assets of her child; and, to help balance the parental scale, the father who expects his child to jump through the hoop with perfect and prompt obedience when he snaps his fingers.

Our method of treating such destructive attitudes is through discussions of the principles involved and by giving didactic advice patiently and tactfully. The psychiatrist would doubtless consider this a crude method but there can be no doubt of its effectiveness so long as we stay clear of deeply rooted conflicts and well developed neuroses, so long as we stay fairly close to the surface, and so long as we keep clearly in mind our aim—to promote sound mental health. And for the sake of the record let it be said that there are many parents who, through the intelligent application of sound principles, do know and practice most of the rules of the game and whose children therefore do have excellent mental health.

But we do not expect our parents to create a letter perfect environment of human relations for their children. We tell them that the tree which is blown about a bit by the wind puts down stronger roots and that the child who must meet and solve a few irritations thereby builds stronger character.

Over and above all and in a much larger sense, as citizens as well as pediatricians, we see clearly that if we want a better world we shall have to inhabit it with better people. If we want to preserve and strengthen our civilization we shall have to improve the science and art and practice of human relations in the oncoming generations. We shall have to help our children grow into truly mature adults with wholesome minds and with moral strength. For sound psychology and sound ethics fit together and dove-tail at every point, and when these are further enhanced by a sound sense of spiritual values, we have done our utmost. If we can keep this ultimate aim sharply in focus the concept of mental health will constantly grow in power, in dignity, and in overriding importance.

*Discussion by CARL A. ERICKSON, M.D., Pasadena*

I enjoyed Dr. Stork's paper very much and I'm sure that everyone can see why he is considered a leader in his understanding of the psychologic side of pediatric practice.

I'd like to emphasize that it is the pediatrician's responsibility to turn out not only a physically healthy specimen but also a person with agreeable disposition and personality.

The origins of this personality stem back into early childhood and, in fact, into infancy. Perhaps cases of suddenly disturbed personality do occur but usually the cause is searched for in the person's earlier history and if we pursue this back all the way we reach infancy. So, as pediatricians we should try to help parents avoid some of the tensions and

frictions that arise between them and the baby which might, if allowed to progress, lead to disturbed behavior later on. Matters such as schedules, feeding, weaning, training, and discipline are likely sources of trouble and it should be the pediatrician's duty to adequately discuss these matters ahead of time so that upsets will be avoided.

We pediatricians should have more training along this line if we are to do a good job because during these early critical years we are usually the only physician that is seeing the child, and it is our advice that is sought in the handling of many problems. We have the Child Guidance Clinics and I suppose that the pediatricians can be thought of as running infant guidance clinics as well as tending to the food and vitamin needs of our patients.



## The Treatment of Cardiovascular Syphilis

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A SURVEY of the modern treatment of cardiovascular syphilis demands consideration of three fundamental principles. First is that cardiovascular syphilis may be almost entirely prevented by the adequate treatment of early syphilis. The second is the avoidance of serious treatment reactions which may incapacitate the patient or cause his death. The third is that to be beneficial adequate doses of the arsenical drugs must be given.

### PREVENTION OF CARDIOVASCULAR SYPHILIS

Adequate treatment early in the course of the syphilitic process offers almost complete protection against the development of cardiovascular syphilis. Consequently this complication would seldom, if ever, be seen if all syphilis could be diagnosed and treated early. Even when treatment is not given until the phase of late latency the degree of protection is very gratifying. Because in recent years many patients have been treated adequately and relatively early in the course of the infection, the incidence of new cases of cardiovascular syphilis is rapidly decreasing.

### AVOIDING SERIOUS TREATMENT REACTIONS

Serious treatment reactions of the Herxheimer type (or therapeutic paradox) usually occur because the patient is given strongly spirochetocidal drugs before being adequately prepared for them. This is

an age in which vigorous anti-syphilitic treatment is commonly used. Such treatment is desirable in all patients having early or uncomplicated syphilis. However, when evidence of organic disease due to syphilis exists and the disease appears to be of such nature that a Herxheimer reaction might be expected, we should proceed with mildly spirochetocidal drugs such as bismuth until danger of a Herxheimer reaction is past.

Cardiovascular syphilis is one of the manifestations of syphilis in which the Herxheimer reaction may be extremely serious or even fatal. This reaction consists of the activation of existing luetic lesions following the initial administration of a spirochetocidal agent such as an arsenical drug or penicillin. The reaction is characterized by vasodilatation and edema at the site of a lesion. In a patient having partial coronary ostial stenosis due to syphilitic aortitis, the edema may produce further narrowing of the coronary ostium or complete coronary occlusion may occur. The result may be an anginal syndrome, heart failure, or death. The same clinical picture, though somewhat delayed, may result from therapeutic paradox. When aneurysm of the aorta is present it is said that a treatment reaction may result in further dilatation of the aorta or even in its rupture, but the author has never seen the latter.

All physicians recognize that the arsenical drugs are strong spirochetocides and that their use may be followed by a Herxheimer reaction. Few, however, think of penicillin as being powerfully spirochetocidal because it is relatively non-toxic otherwise. Penicillin is a powerful spirochetocide and because of this should be used cautiously in patients having

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Read before a joint meeting of the Section on General Medicine and the California Heart Association at the 76th Annual Session of the California Medical Association in Los Angeles, April 30-May 3, 1947.

late syphilis unless they have been properly prepared for its use. This fact should be kept in mind whenever penicillin is used in the treatment of any infectious disease, because syphilis may also be present.

When the foregoing facts are understood there can be only two common causes for the occurrence of Herxheimer reactions. The first cause is that cardiovascular syphilis may be present in the asymptomatic form and hence be unrecognizable, and this might lead to a diagnosis of latent syphilis and over-intensive treatment. The second cause is that the physician may not examine the patient carefully enough to discover obvious cardiovascular syphilis. Unfortunately this latter cause is responsible for the majority of Herxheimer reactions.

Severe reactions can be almost completely avoided by careful clinical study of every patient before any antiluetic treatment is given and by starting the treatment with adequate courses of heavy metal when cardiovascular involvement is found or is even suspected. Every patient who is to be treated for syphilis should be subjected to a complete history taking and physical examination, and ideally should have a careful roentgen study of the heart and aorta. If this is done, most cases of complicated aortitis will be found. Serious reactions may be avoided in treating uncomplicated and hence undiagnosable aortitis by starting treatment in all patients having late syphilis with a long course of a mildly spirochetalid drug such as bismuth.

#### THE ACTIVE TREATMENT OF CARDIOVASCULAR SYPHILIS

The anginal syndrome or cardiac failure when due to aortitis and its complications should be treated as they would be treated in any patient regardless of the cause. Antiluetic treatment should be withheld from patients who are in cardiac failure due to cardiovascular syphilis.

When cardiovascular syphilis has developed to the point where it can be diagnosed, it is commonly undertreated. This unfortunate state of affairs is almost always attributable to the physician's fear of the Herxheimer reaction and its consequences. The reaction need not be feared if the physician knows that the patient has cardiovascular syphilis and treats him properly. No patient being treated for cardiovascular syphilis at the White Memorial Clinic during the last ten years has experienced a Herxheimer reaction, in spite of the fact that we employ larger and more numerous doses of the arsenical drugs than have heretofore been advocated in the literature. This is probably due to the fact that all our patients have been carefully prepared for the use of the powerful spirochetocides.

A number of serious treatment reactions involving the cardiovascular system have been seen. Patients with severe reactions were sent to us by physicians who in most instances had not examined their patients before starting treatment, and hence were unaware of the existence of cardiovascular syphilis. Treatment with arsenical drugs had been started be-

fore the patients were properly prepared. The moral is: Know the patient and then treat him carefully but adequately.

The proper approach to the specific antiluetic treatment of cardiovascular syphilis is a long course of heavy metal which is but mildly spirochetocidal. Bismuth subsalicylate in oil may be given each week for 12 to 16 weeks in doses of 130 mg. to 200 mg.

The iodides seem to be useful in syphilis as in most other granulomatous diseases. Many syphilotherapists start iodides at the onset of bismuth treatment, but the author prefers to wait four to six weeks and then start using saturated solution of potassium iodide in doses of 15 drops three times daily after meals. The dosage is increased gradually so that after about four weeks the patient is taking 60 drops three times daily. Iodides are given with each course of bismuth.

The patient who has cardiovascular syphilis is benefited very little, if at all, by antiluetic treatment unless arsenical drugs are used. The postmortem studies done by Howe<sup>1</sup> demonstrate that there is just as much cellular infiltration in the aortas of patients treated with large amounts of heavy metal as there is in untreated patients. He also showed that there was very little cellular infiltration in the aortas of patients who had received as few as 12 arsenical injections. This demonstrates the need for arsenic and the futility of using bismuth and iodides alone.

After proper preparation with bismuth and iodide, arsenical medication should be cautiously started. The newer arsenical drugs, the arsenoxides, are preferable to the arsphenamines. Mapharsen is the most widely used. The initial dose of mapharsen in common use at present is 10 mg., but the author prefers to use 1 mg. in order to minimize the chance of a Herxheimer reaction. The second dose is usually 5 mg. if the patient has no reaction after the first. The injections are given weekly and may be increased by 5 mg. each week until a dose of 60 mg. is reached. Before each treatment the patient should be questioned to determine if the preceding treatment was followed by angina, dyspnea, tachycardia, palpitation, etc. If any cardiac embarrassment has been experienced the dose must be materially reduced, and then increased more gradually than before. The injections may be given weekly until 20 have been given in the first course. Because the first six doses of mapharsen are very small it is a good plan to give the patient bismuth injections simultaneously.

Most syphilologists recommend that the dose of mapharsen be limited to 30 or 40 mg. Our experience at the White Memorial Clinic during the last ten years causes us to believe that such doses are needlessly small and that they decrease the efficiency of the treatment. Practically all our patients have been given 60 mg. of mapharsen weekly after having been slowly worked up to this dose.

My colleagues in the clinic in treating their patients have used courses of ten weekly injections of bismuth alternated with courses of ten or twelve

weekly injections of mapharsen. My patients have been given mapharsen in courses of 20 weekly injections alternated with courses of ten weekly injections of bismuth. Treatment is given for three or four years continuously.

No serious treatment reaction has been encountered on the vigorous program of treatment described. All our patients seem to have been definitely benefited. None have shown evidence of progression of the syphilitic process in the cardiovascular system. The disease appears to be arrested for the time being at least.

Penicillin is powerfully spirochetocidal and presumably will prove to be useful in the treatment of cardiovascular syphilis. However, it is so new a drug that it has not yet been possible to evaluate it, and consequently its use might well be left to large clinics where it can best be studied. Its ability to produce severe Herxheimer reactions should always be kept in mind.

#### CONCLUSION

1. Cardiovascular syphilis may be almost completely prevented by adequate treatment of early syphilis or even of late latent syphilis.

2. Serious treatment reactions as a rule occur only when patients are given powerful spirochetocidal drugs before being adequately prepared for them by long courses of the mildly spirochetocidal drugs.

3. The physician is usually unaware of the presence of cardiovascular syphilis in the patient who develops a Herxheimer reaction due to overtreatment. This unawareness may be due to the fact that uncomplicated aortitis, and some of the partially developed forms of complicated aortitis, are not diagnosable. Frequently, however, obvious cardiovascular syphilis is overlooked because the patient is not adequately examined. Too many patients are given antisyphilitic treatment as soon as a positive reaction to a serologic test for syphilis is found, even though they have been examined only superficially, if at all.

4. When cardiovascular syphilis is diagnosed it is usually undertreated because the physician fears the Herxheimer reaction. This reaction need not be feared if the patient is properly prepared for the powerful spirochetocides.

5. Adequate doses of the arsenical drugs are essential to satisfactory treatment results.

6. Penicillin has not been adequately evaluated to be routinely used in the treatment of cardiovascular syphilis. It is capable of producing severe Herxheimer reactions.

#### REFERENCE

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## Intraocular Foreign Bodies in Naval Personnel

HUGO LUCIC, M.D., *San Diego*

**PENETRATING** wounds of the eyeball with lodgement of one or more foreign bodies within its deep structures were one of the more important types of injuries seen in navy personnel during the recent war.

Most of such injuries in patients admitted to one of the naval hospitals on the Pacific Coast were incurred in either (1) action against the enemy or (2) at work or in military training, usually in the vicinity of the hospital. Patients wounded in combat usually did not reach the hospital at which the author was stationed until several weeks following the injury and some of them already had received expert care at one or more hospitals along the route. Those injured in the proximity of the hospital, however, usually were seen within a few hours following the accident.

From January 1941 to July 1946 some 95 patients presumably with intraocular foreign bodies were admitted to the hospital. The records of 68 of these were analyzed.

Of the 68 patients with intraocular foreign bodies 40 received injuries in combat and 28 in the course of work or military training. In 35 of the 40 men injured in action the foreign particles in the eyes were presumed to be nonmagnetic. The particles in the remaining five were magnetic. Ten of the 40 men who were injured in action had multiple particles within the same eye and three suffered injury to both eyes. In three of the five cases in which the particles were magnetic they were successfully removed. In two cases the eyes had to be enucleated. A large number of the nonmagnetic particles were small, and as they were apparently well tolerated they were left undisturbed.

Of the 28 men who received injuries at work or in the course of training, 21 harbored magnetic particles, and in 17 of the cases these were successfully removed. In five of the seven cases in which the particles were nonmagnetic, the particles were removed. In three of the 28 cases the affected eye had to be enucleated.

### DIAGNOSIS

**History.** In making a diagnosis of intraocular foreign body a careful history of the injury is of considerable importance. An eye that was injured while the man was exposed to flying particles of hand grenades, land mines, bombs, machine gunfire, or other flying missiles, or while the patient was hammering, drilling, etc., should be suspected of harboring a foreign particle. A careful description of the

tools used and the manner in which the accident occurred help to determine the probable nature of the foreign body.

**Clinical Examination.** Often the wound of entrance, which may or may not be associated with prolapse of the uveal tissue or vitreous, can be seen by ordinary examination. On the other hand, the wound may be so small as to be invisible even with the aid of the slit lamp and corneal microscope. A reduction in intraocular pressure, a shallow anterior chamber, or hemorrhage in the vitreous and lens-lircular opacities are signs which point to an ocular perforation and the possibility of an intraocular foreign body.

In old injuries the chemical effect of the foreign body may be visible. Fragments of copper produce specific changes known as ocular chalcosis. These are seen as a peculiar greenish color in Decemet's membrane and lens capsule, and the changes in the latter produce a picture simulating a sunflower. Steel or iron retained in the eye over a long period slowly oxidizes and the products of oxidation stain the ocular tissues a reddish-brown known as siderosis. This is usually seen clinically in the lens, iris and cornea.

The following case is an example:

### CASE REPORT

A carpenter's mate, aged 21, entered the hospital February 22, 1944, complaining of impaired vision in the right eye. He stated that in 1940 while he was pounding on a nail a piece of steel hit his right eye. He received medical treatment for nine days, and the eye then was apparently well. No x-ray examination was made at the time. On admission to the hospital vision in the right eye was limited to counting of fingers at six inches. The iris appeared greenish-brown in color and there were several dark brown granules dispersed through the subcapsular region of the opaque lens, giving it a dirty-grey appearance and indicating siderosis (Figure 1). Intraocular tension was normal. Roentgen examination revealed a small (1 mm.) metallic particle in the region of the ciliary body. The particle was removed by the anterior route through a small corneal incision. The lens was subsequently needled and final corrected vision was 20/20.

**X-ray Examination.** An x-ray examination is indicated whenever there is suspicion that a foreign body has struck the eye even though a careful clinical examination reveal no sign of injury. Small foreign bodies may not show in an x-ray film taken in one view only. In such instances several different exposures should be made, as advocated by Thorpe.<sup>5</sup> When a particle is not entirely radiopaque or is so small as not to show against the shadows of the bones, it can sometimes be demonstrated by the bone-free method of Vogt<sup>2</sup> provided it is located in the anterior segment of the eye. This is accomplished by using small

Read before the Section on Eye, Ear, Nose and Throat at the 76th Annual Session of the California Medical Association in Los Angeles, April 30-May 3, 1947.

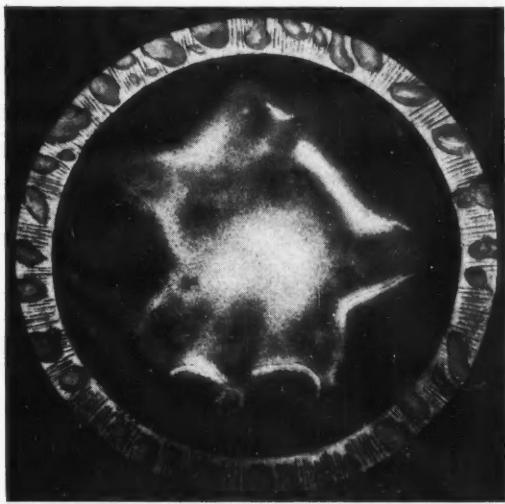


Figure 1.—Iris and lens showing siderosis.

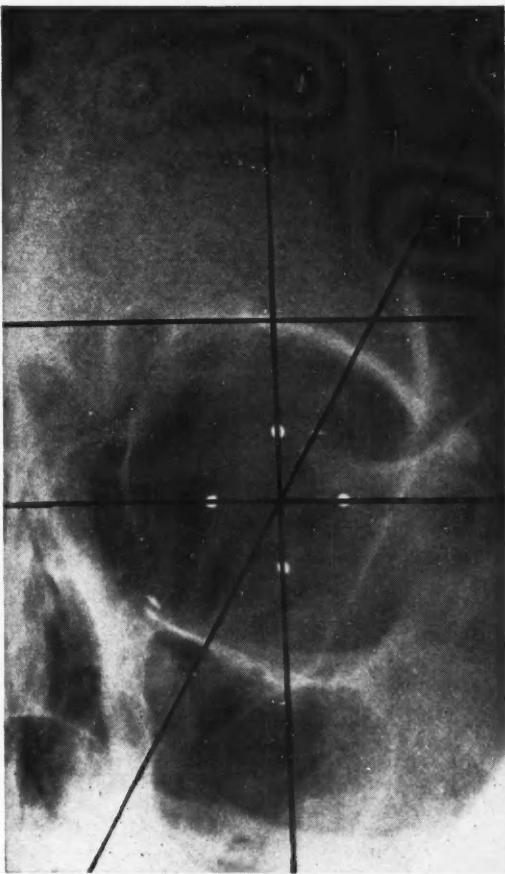


Figure 2.—Roentgenogram with lines for localization of foreign body in frontal plane according to Comberg.

dental films pushed deeply into the orbit at the nasal angle, with the orbit then photographed from an anterolateral position. To obtain a better exposure the eye may be made to protrude by retrobulbar injection of 3 cc. of a 1 per cent solution of procain hydrochloride.

**Localization.** Before extraction of a foreign body from the eyeball is attempted, its exact position in relation to the globe should be determined. This is imperative if the particle is nonmagnetic, less important if it is magnetic and its size and shape known.

There are several satisfactory methods of localization. We have employed Comberg's method.<sup>3</sup> A contact lens with four lead marks is placed over the cornea and two exposures are made, one exactly in the visual line (Figure 2) and one at right angle from the first exposure (Figure 3). Location of the foreign body with reference to the central point then is easily determined by drawing lines between the shadows of the marks on the plate. The meridian of the globe is found by extending the line from the foreign body to the central point to meet the horizontal drawn on the chart and the distance of the particle from the plane of the limbus is easily determined in

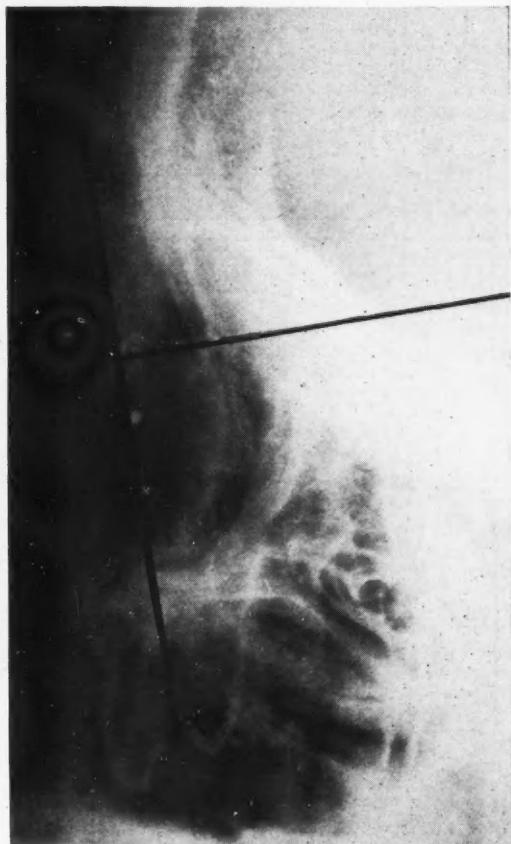


Figure 3.—Lateral view.

the lateral view. The results are then plotted on special charts (Figure 4).

Comberg's method is highly satisfactory in most cases, but occasionally error creeps into the picture and the foreign body is localized 1 or even 2 mm. from its true position. This, of course, is a serious mistake when dealing with nonmagnetic particles or when a particle is close to the periphery of the globe so that it appears to be extraocular when it is actually in the eye, or vice versa. The latter difficulty can often be eliminated by injecting air into Tenon's space to create a contrast between the globe and the surrounding tissue. The chief objection to the Comberg lens is that it sometimes slips off the cornea, thereby introducing a serious error in localization. Thorpe<sup>6</sup> has recently modified the Comberg lens to obviate this objection by drilling suture holes in the periphery of the lens so that it can be anchored.

If more than one foreign particle is present, and especially if one is imposed upon another, localization of each in reference to the globe may be difficult or even impossible. The following case report is illustrative:

#### CASE REPORT

The patient received injuries about the face and both eyes due to a hand grenade explosion. A small particle of shrapnel was removed from the left eye at another hospital. Eight weeks later, on admission to the hospital at which the author was stationed, vision in the right eye was 20/200 and in the left eye 20/20. Except for a small corneal scar, an anterior synechia, and an irregular pupil, the left eye appeared normal.

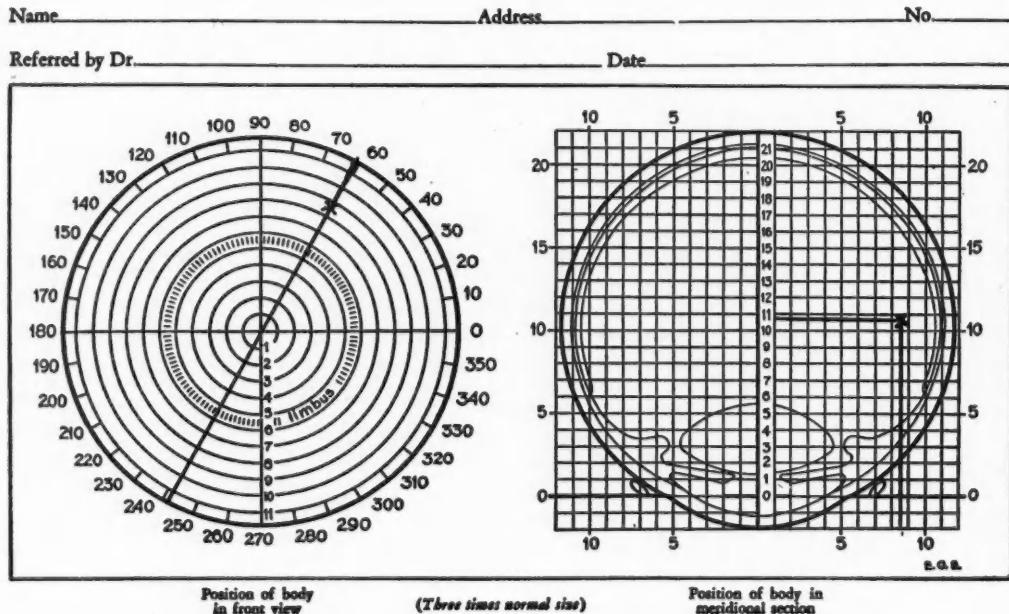
The right eye presented a grey, organized mass in the lower part of the fundus and a hazy vitreous. Roentgen examination disclosed several metallic particles in the region of the eye, two of which, although appearing to be within the globe, were difficult to localize because of multiplicity of shadows in the two views.

A foreign body in the vitreous which shifts with the position of the head presents another problem in localization. Two such cases were seen among the 68 patients. In one of these the particle was magnetic and the lens was already opaque. It was easily extracted by the anterior route. In the second the particle, which was visualized through the pupil, moved freely in the vitreous with each movement of the eye. It was nonmagnetic and it was removed with a forceps under direct visualization.

#### TREATMENT

It may be stated categorically that any intraocular foreign body should be removed as soon as possible unless its removal involves more danger than its retention in the eye. Details of the surgical procedure and medical treatment will depend on several factors, such as the age and extent of the injury, the size, shape, nature and location of the particle.

If the injury is recent, the patient is given prophylactic doses of sulfadiazine or penicillin and injections of typhoid antigen intravenously. Antitetanic serum is often indicated. Atropine is used in most cases unless contraindicated by primary glaucoma.



SUPERIOR TEMPORAL QUADRANT, LEFT EYE. 62 DEGREE MERIDIAN.  
8.6 MM. FROM AF AXIS. 10.6 MM. POSTERIOR TO LIMBAL PLANE. 1.8 MM. IN DIAMETER.

Figure 4.—Comberg's charts for plotting localization in the two views.

If severe intraocular infection develops, with loss of light projection, removal of the eye is advisable.

As magnetic foreign bodies usually can be removed without difficulty while nonmagnetic particles present an entirely different problem, it is important to know before operation whether the particle is magnetic or not. Theoretically a radio-amplification device, such as the Berman Locator<sup>4</sup> would be an ideal instrument to use in cases of doubt. If such an instrument is not available, other methods of differentiation must be used. As patients with shrapnel injuries of the eyes usually had similar particles imbedded about the face, these were removed and tested for magnetic reaction. In the absence of such particles we had to resort to the use of the magnet for differentiation.

Magnetic particles may be removed by the anterior or the posterior route, the choice depending on the size and shape of the foreign body and the damage suffered by the eye. The author believes that when the foreign body is small, when a cataract is already present or when the particle is located in the region of the macula, the anterior route should be used, and that large, jagged particles should be removed by the posterior route, especially if the lens is clear.

In extracting foreign bodies by the anterior route the giant magnet is used and exact localization is not necessary. The pupil is dilated widely and the magnet is applied first at about 12 inches from the cornea, using the least amount of current available. The current is turned on intermittently and is increased gradually. The magnet also is slowly brought closer to the cornea. If the foreign body is attracted by the magnet the iris is seen to bulge forward and the patient will usually experience some pain. By careful manipulation of the magnet the particle is brought into the anterior chamber and is then extracted with the hand magnet through a corneal incision. The corneal incision should be so made as to avoid the formation of a large shelf. This can be accomplished more easily by using a cataract knife rather than a keratome.

Sometimes magnetic particles can be extracted by the anterior route several years following the injury. (Case 1, Figure 1.)

Extraction by the posterior route requires an incision in the sclera usually as near the foreign body as possible unless there is a fresh scleral wound already present. The incision should be meridional and large enough to allow the largest diameter of the particle to pass freely. If the incision need be large, an intrascleral suture should be inserted before completion of the incision. To prevent retinal detachment, diathermy coagulation should be employed around the incision. When the particle is in the vitreous, an equatorial incision may be made over the flat portion of the ciliary body to avoid making a hole in the retina as advocated by Verhoeff<sup>7</sup> or a trephining hole as used by Barbour and Fralick.<sup>1</sup> The incision may be made also at the ora serrata along the anatomical attachment of the retina. The tip of the hand magnet is then introduced into the

eye for a distance of about 2 mm., the current is turned on and the particle extracted. After extraction of any intraocular foreign body, atropine is used, the eye is covered and the patient is kept quiet for several days. The following case illustrates this method of extraction:

#### CASE REPORT

The patient was hit in the left eye by shrapnel. On admission to the hospital a month later, vision in the left eye was 20/40. There were no external signs of injury but the vitreous presented a particle which appeared to be a foreign body. The lens was clear. X-ray examination showed an intraocular, metallic foreign body measuring approximately 2 mm. in diameter and located in the 62 degree meridian in the superior temporal quadrant, 8.6 mm. from the visual axis and 10.6 mm. posterior to the limbal plane (Figures 2, 3 and 4). The sclera was exposed in the indicated region, an equatorial incision 4 mm. long was made half way through the sclera 10 mm. from the limbus, a mattress suture was inserted and the incision was completed to the choroid. Diathermy coagulation was used around the incision and the choroid was incised with a sharp cataract knife. The tip of the hand magnet was inserted into the wound, the foreign body was extracted without difficulty and the incision was closed. Subsequent progress was uneventful and the vision remained 20/40.

Nonmagnetic particles when visible in the anterior chamber may be extracted with special forceps through a corneal incision. Similar particles in the posterior segment are difficult to remove and it is often less dangerous to leave them undisturbed than to attempt their removal. Small particles of glass and other inert substances are often well tolerated by the eye and may be retained for many years without much damage to vision. We have left undisturbed a majority of the eyes harboring tiny particles of nonmagnetic shrapnel which had not caused any reaction during the period of observation of six months or longer.

Particles of copper are notoriously poorly tolerated and whenever possible should be removed. Such particles when visible in the vitreous may be removed with special or improvised forceps, as illustrated by the following case:

#### CASE REPORT

The patient received an injury to the left eye when a copper blasting cap exploded in his hand. Vision in the injured eye was 20/70. The vitreous was somewhat hazy due to the presence of blood, but a tiny, glistening particle, presumed to be copper, could be seen floating in its anterior portion. The anterior chamber and intraocular pressure were normal. There was no visible evidence of a wound. Roentgenograms did not show evidence of an intraocular foreign body, but two particles were present in the soft tissues. Application of the giant magnet did not attract the intraocular particle. Two days after the injury the blood in the vitreous had absorbed sufficiently to allow good visualization of the foreign body.

The particle was removed with a Kalt capsule forceps after obliterating the curve of the forceps. The sclera of the superior temporal quadrant of the globe was exposed, a small equatorial incision was made halfway through the sclera in the region of the ora serrata, a suture was placed through both lips of the incision and the incision was completed into the vitreous. The forceps was introduced into the vitreous and under direct visualization the particle was

grasped and extracted. It proved to be a particle of copper measuring 1 mm. in diameter. The patient was given prophylactic injections of typhoid antigen intravenously and sulfadiazine orally. He was discharged from the hospital three weeks later with visual acuity of 20/20. Three months following the injury vision was 20/15 and the eye appeared normal.

Large particles of copper when embedded in the deep structure of the eye will certainly cause subsequent reaction and should be removed. The following case illustrates this point and shows how a large particle may be removed from the ciliary body:

#### CASE REPORT

The patient was struck in the right eye by a piece of wire. He was treated at the time and when the eye was free of inflammation was discharged to duty with vision of 20/20. According to the history an x-ray examination at that time revealed no foreign body. Approximately six months later, vision gradually became blurred and the patient was admitted to the hospital 15 months following the accident. Vision in the affected eye was limited to ability to distinguish hand movements. There were cells in the anterior chamber, and the lens was opaque and dislocated. Intraocular pressure was normal. X-ray examination disclosed a foreign body 11 mm. long located in the inferior temporal quadrant, in the ciliary body, somewhat concentric with the limbus (Figure 5). A meridional incision 5 mm. long was made over the

foreign body which was engaged with a blunt iris hook and extracted.

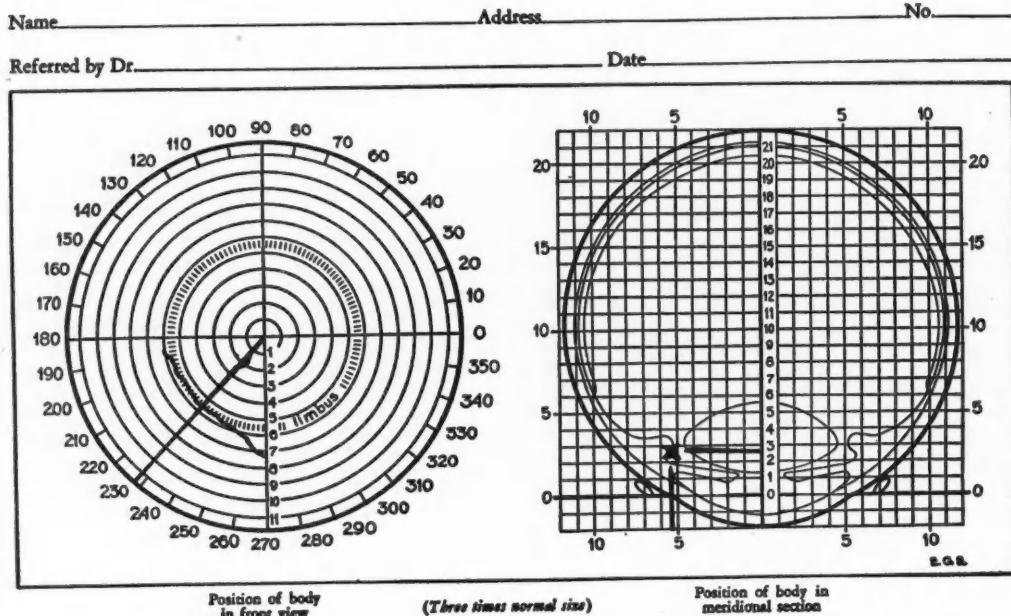
Occasionally an intraocular foreign particle may spontaneously work out to the surface through the original wound or through the surgical incision following an unsuccessful attempt at removal, as illustrated by the following case:

#### CASE REPORT

The patient was hit in the eye by a particle of shrapnel. He entered the hospital eight weeks later, at which time vision in the injured eye was 20/70. X-ray examination disclosed a metallic particle in the inferior temporal quadrant, 6.8 mm. from the visual line, 3.2 mm. posterior to the limbus (Figure 6). Details of the fundus could not be made out due to the presence of blood in the vitreous. The indicated area was exposed, a 5x2 mm. scleral flap was raised and the hand magnet applied over this area, without success. The reaction in the eye subsequently quieted and vision improved to 20/40. Six months later, the particle was seen to bulge under the conjunctiva and it was removed with a forceps. It was nonmagnetic.

Undoubtedly many nonmagnetic particles may be successfully removed from the eye with the aid of the biplane fluoroscope or the ocular endoscope, but the author has used the former in one case without success and has had no experience with the ocular endoscope.

Chart for Roentgenographic Localization  
of Foreign Body in Eyeball with Contact Lens



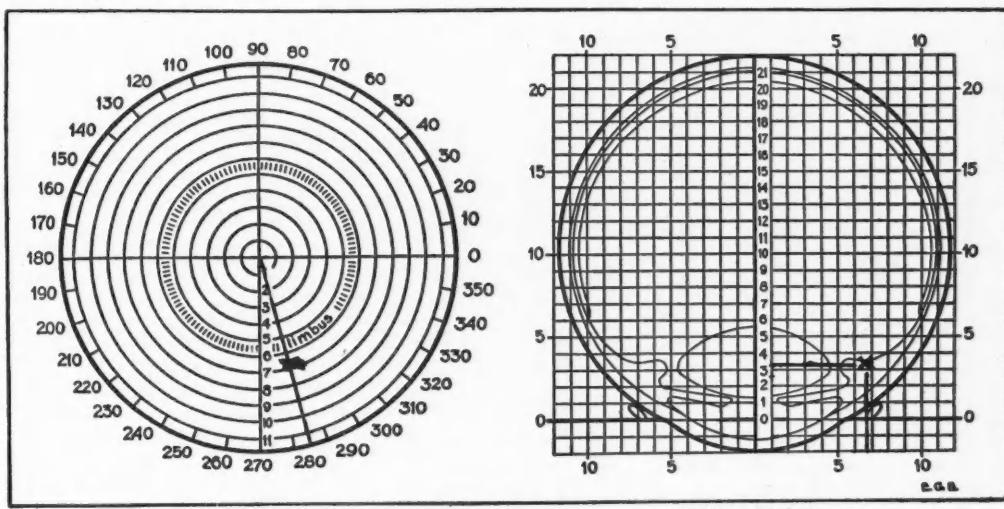
INFERIOR TEMPORAL QUADRANT, RIGHT EYE. 233 DEGREE MERIDIAN.  
5.4 mm. FROM AP AXIS. 2.7 mm. FROM PLANE OF LIMBUS.  
11x0.5 mm. IN DIAMETER.

Figure 5.—A long piece of copper wire localized in the ciliary body.

**Chart for Roentgenographic Localization  
of Foreign Body in Eyeball with Contact Lens**

Name \_\_\_\_\_ Address \_\_\_\_\_ No. \_\_\_\_\_

Referred by Dr. \_\_\_\_\_ Date \_\_\_\_\_



**INFERIOR TEMPORAL QUADRANT, LEFT EYE.**  
**6.8 mm. FROM AP AXIS. 3.2 mm. POSTERIOR TO PLANE OF LIMBUS. 1 mm. IN DIAMETER.**

Figure 6.—Nonmagnetic foreign body localized in the ciliary body, worked out spontaneously.

Small foreign bodies located in the crystalline lens, if nonirritating, like a piece of glass or aluminum, should be left undisturbed as they may not cause progressive opacification. A patient was admitted to the hospital three days following multiple injuries received in combat. In the cortex of the left lens, just above the center, there was a glistening particle which was presumed to be aluminum. The path made by the particle could be traced through the eye by the scar in the cornea, the hole in the iris and the anterior capsule of the lens. Vision in this eye was 20/40. The particle was considered nonmagnetic and no attempt was made to remove it. Six months later vision in this eye was 20/20 and there was no sign of active inflammation in the eye.

Any penetrating injury of the eye is a potential cause of sympathetic ophthalmia. It is remarkable that not one case of this dread disease has occurred among perhaps 150 patients with penetrating in-

juries that were observed during the entire war at one of the largest naval hospitals.

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## Environmental Survey in the Diagnosis of Allergic Disorders

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A SURVEY of the patient's environment is a necessary although frequent minimized adjunct in the diagnosis of allergic disorders. This involves a consideration and evaluation of possible pertinent allergic offenders in the patient's immediate surroundings. In most practices this information is secured by questioning the patient during the initial interview. However, in the experience of the author, this procedure is unsatisfactory because the patient often is unaware of the details of his environment without preliminary study and thought. Patients, as a rule, do not know the composition of their upholstered furniture, mattresses and pillows; they cannot identify trees and weeds in the neighborhood of their homes; they do not know the exact ingredients of the vitamin pills they take or of the canned food they eat. In a seasonal pollen allergy these details may not appear important, but in an obscure perennial rhinitis, persistent asthma or prolonged atopic eczema, they may be critical.

A more satisfactory method of obtaining the required data, we have found, is to submit a detailed questionnaire to the patient for completion at home after consultation with other members of the family and examination of manufacturers' labels on household articles. The ideal method, one that we have found to be increasingly necessary in our clinic, is that of the physician or a trained member of the staff visiting the patient's home and making a detailed inventory of the environment, searching for allergens which may be related to the patient's complaint. It is the purpose of this paper to outline a systematic method of conducting such a survey and to discuss in some detail the factors involved. The plan outlined in this discussion may be made the basis of a questionnaire for the patient to complete, or may be used as a guide by the person actually making the physical survey.

### NEIGHBORHOOD

The location of the house is very important. The house on a busy thoroughfare with much traffic on it will be subjected to invasion by fine dust particles, while one situated in the center of a four-acre wooded tract will be invaded by tree, grass and weed pollens. The author recalls at least one case in which the patients' asthma was immediately relieved when he moved from a neighborhood in the vicinity of a furniture factory. Another patient was cured of a constantly running nose when she moved from a neighborhood near a railroad track along which an average of 12 smoke-belching locomotives passed daily.

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The importance of identifying trees, weeds and grass in the vicinity of the home is well known. Allergic symptoms of one patient were immediately ameliorated when the weeds on a vacant lot adjacent to her home were burned. Another patient with olive tree sensitivity was surprised to learn that the magnificent tree on her front lawn was an olive and was quite pleased when her symptoms disappeared on its removal.

If the patient lives on a farm one must consider the crops planted and should search for rusts and smuts.<sup>6</sup> A farmer with severe hay fever during the threshing season was greatly relieved of his symptoms by hyposensitization with corn smut. Recently the author had occasion to study a farmer with asthma who was found sensitive to an autogenous dust extract prepared from dust collected in his barn. Having the patient avoid the barn as much as possible and treating him with the barn dust produced great relief of symptoms. Animals encountered on the farm, too, should not be overlooked. Last year the author studied a dairy farmer who was exquisitely sensitive to cattle hair. This case posed a problem which was solved by change in occupation.

### THE HOUSE

The age and state of repair of the house, the author finds, is a factor which the patient and many doctors overlook. A damp house with decayed wood in its framework is likely to be a cause of trouble especially in mold-sensitive patients.<sup>1</sup> Most patients cannot associate common mildew with their allergy. Some time ago the author interviewed one patient who had traveled and lived in all sections of the country in search of a warm spot where, he felt, his asthma would be better. This patient could not understand why his asthma was worse in Florida until it was pointed out to him that he was sensitive to fungi which were prevalent in that tropical climate. In another case seen by the author, the patient's hay fever was at its worst in the autumn when the heating system of his house was used for the first time. The cause of the disease became obvious when a visit to the home revealed a very damp basement with rotted wood piled up in it and a very efficient forced air heating system which disseminated clouds of fungi into the patient's bedroom. The method of cleaning the house, too, may be a deeply rooted habit and appear unimportant to the patient. Thus an associate reports a miraculous cure in a patient by mere substitution of a vacuum sweeper for a broom.

### BEDROOM

After considering the neighborhood and the general aspects of the house, the next step is to examine individually the important rooms within the house.

Because the patient spends more consecutive hours in it than in any other room in the house, our practice is to survey the patient's bedroom first. Dust as an antigen in the production of allergic symptoms is well known,<sup>3</sup> but few people realize that it can be found in such hidden and overlooked spots as tops of windows and door casements, curtains and drapes, the edges of rugs, venetian blinds, pictures, wall brackets, knick-knacks and candelabra. Dust often lurks in the coils of spring mattresses, behind dressers and on steel beds. Our practice has been to inspect the room much as a Navy officer does during his weekly inspection, running a finger over inaccessible and overlooked areas in search of dust. In our experience, the most common hiding places of dust in bedrooms are in the coils of bedsprings and in closets where seldom-used clothes hang.

Wool is another allergen that is common as a cause of allergic symptoms. That blankets are woolen is well known to most patients, but it is not so commonly known that common domestic rugs are made of wool. Both can produce symptoms. One patient recently was relieved of major symptoms by substitution of a cotton rug and removal of several wool sweaters found hanging in the closet. Rug and carpet pads are usually made of cattle and horse hair or of jute. As all are capable of producing symptoms they may have to be eliminated. Chenille rugs often contain cow hair while Chinese and other oriental rugs are combinations of wool, cow hair and even dog hair.

Mattresses, which are usually made of cotton linters, horse hair and pig hair, may cause symptoms in a patient. The common "inner spring" mattress is primarily composed of cotton linters. These are usually inadequately covered and, especially if old, can be the cause of symptoms. Some time ago in our clinic we cultured a series of fragments of cotton removed from inner spring mattresses and obtained almost pure cultures of several fungi.

Pillows, of course, are filled with feathers. The more expensive pillows are filled with down (goose feathers) while the less expensive are filled with varying proportions of chicken, duck and turkey feathers. The age of the pillow should be considered. On exposure of a Petri dish alongside a bed overnight we were able to identify feathers in surprising quantities. Culture of this material on enriched medium resulted in a lush growth of molds. One can readily see what effect a good night's sleep on a soft old feather pillow will have on a patient sensitive to feathers or mold. Kapok, too, we found by similar investigative methods was not only a good allergen, but also an excellent medium for fungus growth.

#### LIVING ROOM

In the living room also the dust problem must be scrutinized and the hiding places examined. Fireplaces which are not cleaned often are great repositories of dust. As in the bedroom, rugs, rug pads and furniture upholstery materials must be considered. Furniture covering may be any of a number of ma-

terials, the most important from the allergist's point of view being wool and mohair. Mohair is made of goat hair and is a common constituent of pluses, velvets and velours. Silk which may be used in covering furniture should not be overlooked as a cause of allergy. In considering silk one should not be misled by such terms as faille, satin, foulard, pongee, taffeta and jersey, which are all primarily silk.

The obvious question at this point is, "How is one to know what the living room furniture is made of?" The author made a visit to a major furniture store recently and examined manufacturers' labels on upholstered furniture and mattresses. Many states have laws requiring the manufacturer to attach a tag to each article of such furniture stating the exact composition of the concealed materials used in its manufacture. Thus a typical label on a couch read, "Concealed Materials Are All New Materials. Contents: Body—Horse Hair, 12½ per cent; Hog Hair, 87½ per cent, together constituting 50 per cent Cotton Felt, 50 per cent Cushions—Duck Feathers 75 per cent, Down 25 per cent." If there are no tags, or if the patient had removed them on purchase, the general composition as outlined here will fit most articles. The importance of the composition of upholstered furniture was recently brought to the attention of a member of our clinic whose patient, sensitive to hog hair, was relieved of symptoms upon buying a new couch.

The fireplace should be scrutinized carefully, not only for dust but for the type of wood burned. A former associate, some years ago, reported a case of severe asthma resulting from wood smoke.<sup>4</sup> Other factors which one looks for in the living room are artificial leather on furniture and heavy coating of furniture polishes and waxes. These all may contain large amounts of linseed oil, which is not an unusual cause of allergy.

#### BATHROOM

A list of all the drug and toilet articles found in the medicine cabinet should be made because patients too often forget the medicines they take and the cosmetics they use. Hair brushes, shaving brushes and tooth brushes should be considered in the light of possible animal hair allergy. One patient who was sensitive to animal hair had his entire allergy problem solved by mere substitution of an electric razor. Common proprietary medicines and toilet articles may contain an allergic ingredient of which the patient is not aware. Orris root, an important allergen, is no longer a common constituent of face powders since its allergic importance has been pointed out to cosmetic manufacturers. However, it is still used as a carrier or binder for odors in perfumes and therefore may be found in perfumed toilet articles. The so-called allergen-free cosmetics and face powders are mainly free from orris root and therefore may be as allergenic as most of the commercial powders. The importance of hidden ingredients in medicines was brought to the attention of an associate very strikingly when a patient, exquisitely sensitive to milk, continued to have asthma

in spite of a rigid milk-free diet. In this case it was discovered after prolonged investigation that the ephedrine and aminophyllin capsules prescribed for symptomatic relief contained lactose.

Powder puffs may contain sheep or lamb wool, though the majority of the inexpensive ones used by most women are made of cotton. Linoleum on bathroom floors is commonly treated with linseed oil, and in some cases an oiled silk shower curtain may be the cause of the trouble.

#### KITCHEN

A list of all the foods in the kitchen cupboards and in the refrigerator should be made, mainly because the patient forgets what he eats. Patent prepared and packaged foods must be suspected primarily because of the hidden allergens they contain. Although manufacturers' labels required by food and drug laws are adequate, patients are not label-conscious and actually do not know what they eat. A discussion of the hidden constituents in packaged foods could be almost limitless. Several examples, however, are in order and will serve the purpose of emphasizing their importance. Corn, in the experience of the author, is the most ubiquitous allergen found in commercially packaged foods. It is used in almost all syrups, candy bars, ices, sherbets, ice cream, tenderized ham, canned fruits and baking powder. Corn is used in chewing gums, in bourbon and other whiskies, in beer and ale, and in carbonated beverages. Unless there has been a change in formula recently, such well known products as Welch's Grape Juice, Jello, Mull-Soy, Pablum, Linit, Kix, Mazola and Karo contain corn products. Wheat, egg and milk sensitivity are the most common and the detection of these ingredients in commercial food products often is difficult. A visiting lecturer, some years ago, described a patient who was sensitive both to coffee and to wheat. This patient used Postum as a substitute for coffee and continued to have symptoms until it was discovered that Postum contained wheat.

Other common allergens found in kitchens are oil-cloth and artificial leather which are treated with linseed oil. Brushes and brooms are made of wheat, rye, barley and rice (straw) and of animal hair, mainly that of hog, horse, goat, sheep, and camel. Laundry starch is made primarily of corn, but may be made of wheat or rice. Candles are usually made of cottonseed oil; twine and rope are made of animal hair, cotton linters, straw and flaxseed.

#### CLOSETS

Closets have already been mentioned as repositories of dust. In many homes closets serve as catchalls and therefore may contain any number of possible allergens. Fur coats and fur collars on cloth coats should be regarded with suspicion and the fur must be identified. It should be pointed out that rabbit pelts are commonly plucked, sheared and dyed in imitation of more expensive furs such as seal, fox, squirrel, mink, beaver, leopard, and sable. These imitations usually parade under trade names with

the suffix "ette" or "ine" added such as Beaverette and Squirreline; or they may be identified by the addition of modifying proper names, becoming Belgian beaver, French leopard, French sable and Australian seal. The author recalls one case in which a lifelong friendship was almost terminated when it was pointed out to a patient in the presence of a friend of hers who wore a French beaver coat, that a sensitivity to rabbit hair caused her symptoms to develop in her friend's company.

Among the articles commonly found in closets which may be related to the patient's allergy are felt hats, commonly made of various animal hairs, and patent leather shoes, which are treated with linseed oil. Clothes moths found in the closet of a patient have been reported as a cause of asthma.<sup>5</sup>

#### MISCELLANEOUS

The plan outlined to this point should be extended to include other important rooms in the house such as den, sun parlor, nursery, work room and music room. A patient with severe atopic dermatitis was cured when he was forbidden entrance into a workroom where his son made furniture as a hobby. The author remembers a patient with a sunroom filled with plants. The only difficulty was that the patient had an eczematous sensitization to philadendrum. In this connection the author remembers the story a prominent dermatologist enjoys relating about the patient who had an eczematous dermatitis of the hands which was suspected of being caused by a plant in her room, most likely primrose. For more than a year the patient insisted that she had no plants in her home. Finally, after a year of unsuccessful treatment, a new associate in the office asked if she had any plants near her house. "Oh yes," was the glib reply, "I have a primrose plant in a window box just outside my living room which I trim and water every day."

Some miscellaneous allergens do not fit into the plan of room-to-room survey. Among these are paint and plaster walls.<sup>2</sup> Paints and varnishes contain linseed oil or corn oil or both, while plaster often has animal hair incorporated in it. Roofing tar has linseed oil added. Allergy to these is usually to the fresh paint, plaster and varnish rather than to that which has been in place for some time. Painter's asthma is not rare.

Although this is not strictly a part of the physical survey of the environment, mention must be made of the effect of the psyche on allergic symptoms and how a visit to the home may often disclose conflicts which are not apparent during the office examination. During the visit to the home the trained observer may discover the attitude of the patient toward the medical regimen. In the case of a child, one can note the relationship between the child and other members of the family and whether the child is made self-conscious by his running nose, red eyes or wheezing breathing. The author can remember visiting the home of an 11-year-old asthmatic in search of offending allergens. Casually looking at the music

on the piano and noting that there were two sets of almost identical complicated finger exercises, the author was able to ascertain, through questioning, that the patient competed with her elder sister for proficiency in music. Attacks in this case could be directly connected with visits to the music teacher.

#### SUMMARY

A systematic plan for the survey of the environment surrounding an allergic individual has been outlined and discussed in detail. Though not complete this plan can be made the basis of a questionnaire to submit to the patient, or can be used as a guide by the person making the actual survey.

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## Further Experiences With Pontocaine-Dextrose Ephedrine For Spinal Analgesia

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**N**OWHERE in the realm of anesthesia is so much accomplished by so little as in spinal analgesia. The few milligrams of drug with which profound degrees of analgesia over extensive areas of the body is achieved would be of inconsequential effect if applied elsewhere. The first spinal injection, consisting of 2 cc. of a 3 per cent solution of cocaine (60 mg.), was given for therapeutic purposes by Corning in 1885.<sup>5</sup> Thirteen years later Bier submitted to the injection of 2 cc. of a 1 per cent solution of cocaine into his own spinal canal.

The dosage of drugs in current use varies with the drug used, the length of the operation and the experience of the anesthetist. In 1928, Sise<sup>9</sup> used from 200 to 300 mg. and occasionally as much as 400 mg. of procaine. In 1935 he introduced the pontocaine-glucose mixture,<sup>10</sup> advocating doses ranging from 10 to 14 mg. for perineal surgery to as much as 20 mg. for procedures in the upper abdomen.

For many years it has been recognized that complications in spinal analgesia are almost directly proportional to the size of the dose of the anesthetic agent. It is not surprising, therefore, that although the quantities of the drug required are now rela-

tively small, efforts should be directed toward developing means of reducing the dosage still further.

Vasoconstrictor drugs were added to the spinal anesthetic mixture very early in the history of spinal analgesia in an effort to prolong the action of analgesia and to make possible the use of smaller doses of the agent. Recent techniques have been introduced by Prickett, Gross and Cullen,<sup>7</sup> who report the use of a procaine-epinephrine mixture resulting in a marked increase in the duration of the analgesia. Their work was based on the well known fact that epinephrine by its vasoconstrictor effect prolongs the action of a local anesthetic agent by decreasing its rate of absorption. The objection has been raised that epinephrine might produce damage to the cord and nerve roots through excessive vasoconstriction and resultant ischemia.<sup>1</sup> This consideration led others to substitute ephedrine since its action as a local vasoconstrictor is not so powerful.<sup>2</sup>

The most recent report on the use of ephedrine intrathecally is that of Potter and Whitacre.<sup>8</sup> They review the work of Jianu and Moisescu<sup>3,4</sup> who in 1932 and 1933 added cardiazol-ephedrine to nupercaine and achieved satisfactory analgesia with as little as 2 mg. of the anesthetic agent. They also cite the work of Romberger<sup>9</sup> who increased the duration of analgesia by 40 per cent or more with mixtures of procaine and ephedrine intrathecally. Potter and Whitacre reported a series of 1,114 patients, half of

Read before the Section on Anesthesiology at the 76th Annual Session of the California Medical Association in Los Angeles, April 30-May 3, 1947.

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whom received pontocaine-dextrose-ephedrine mixture, the other half receiving only pontocaine-dextrose. This report covers only herniorraphies, cystoscopies and operations on the rectum, vagina and lower extremities. They did not use this procedure for intra-abdominal operations.<sup>11</sup> They concluded that ephedrine does prolong the action of pontocaine. Also with this technique it is possible to use smaller doses (as much as 30 per cent less) of pontocaine and still achieve comparable degrees of analgesia, which they felt might increase the margin of safety. These workers noted no untoward effects or serious complication attributable to the use of this combination of agents.

Encouraged by these impressive results, we undertook to determine whether this technique might not be used with benefit in intra-abdominal operations. This presentation is a report of our experience with intrathecal injection of mixtures of pontocaine, dextrose, and ephedrine, in giving 167 anesthetics, of which 103 were for intra-abdominal operations.

#### TECHNIQUE

In the beginning we followed the technique employed by Potter and Whitacre, i.e., mixing equal parts by volume of 1 per cent pontocaine, 10 per cent dextrose and 5 per cent ephedrine. Using 1 cc. each of these agents results in a mixture containing 10 mg. of pontocaine and 50 mg. of ephedrine in 3 cc. of solution. Therefore, multiplying the required dosage in mg. of pontocaine by 0.3 will yield a figure which represents the number of cc. of solution which should remain in the syringe to be injected into the subarachnoid space without further dilution. In this solution the ratio of pontocaine to ephedrine is 1 to 5.

We started by using doses of 5 or 6 mg. of pontocaine but soon found that in intra-abdominal procedures we were unable to obtain sufficiently high levels of analgesia even when the patient was placed in sharp degrees of the Trendelenburg position. The one exception to this failure is in cesarean section, in which higher levels are notoriously more easily secured with smaller doses than in other abdominal operations. The dosage was then increased to 8 mg., which appeared to be adequate in the majority of cases. In a few cases 10 mg. was given.

In an effort to learn whether or not comparable effects might be secured with smaller dosages of ephedrine, we began decreasing the ratio of 1 mg. of pontocaine to 5 mg. of ephedrine and finally decided upon that of 1 mg. of pontocaine to 3 mg. of ephedrine, which appears to be quite as effective. This we secured by mixing 1 cc. of 1 per cent pontocaine, 0.6 cc. of 5 per cent ephedrine and 1.4 cc. of 10 per cent dextrose. This mixture thus contains 10 mg. of pontocaine and 30 mg. of ephedrine in 3 cc. of solution. The volume injected is dependent upon the desired dosage of pontocaine and is arrived at as in the original technique. It would be possible to draw into the syringe just the desired dosage of each of these drugs but there is less error in measuring the larger dosages and discarding the portion not needed.

In all cases the lumbar puncture and injection

were made with the patient in the lateral position, the site of the puncture being either L2 or L3. The solution was injected at a little more than average rate, the injection taking from 4 to 6 seconds. No barbotage was employed to obtain the desired level. Immediately following the injection of the agent the patients were placed in the supine position, with a pillow under the head and shoulders and tilted to a 10 degree Trendelenburg position, which effectively pools the agent in the mid-thoracic region, since the anesthetic mixture is hyperbaric. Levels of anesthesia up to T4 or T5 are thus secured.

#### CLINICAL RESULTS

The patients were not selected, but were taken in consecutive order and chosen only because they were considered suitable for spinal anesthesia. They ranged in age from 18 to 82 years. There were 115 females and 52 males. The previously described technique of mixing and injection was employed in all cases. Our modification of decreasing the dosage of ephedrine was used whenever the selected dosage of pontocaine was more than 5 mg.

The maximum dose of 10 mg. pontocaine was administered to only eight patients, while 107 received 8 mg. (Table 1). In 125 instances the dose of ephedrine was approximately 25 mg. while the 50 mg. dose was given only three times. There were six cases in this series in which little or no analgesia was secured and in these results were classified as unsatisfactory. These failures we felt to be due to technical errors that reasonably may be expected in a teaching department. As is shown in Table 2, we found it necessary to supplement the spinal anesthetic in 47 patients because of pain. In 33 of these cases the supplementation was done before an elapsed time of one and one-half hours and the results should be considered as not wholly satisfactory. Some of these failures might legitimately be charged to the "trial and error" method by which we arrived at the optimum dosages. Twenty-eight patients received a

TABLE 1.—Showing the various surgical procedures and the number of cases of each type. The actual number of patients receiving the various doses of pontocaine is also shown.

Surgical Procedures	Dosage of Pontocaine Milligrams									
	3	4	5	6	7	8	9	10	Total	
Pelvic Laparotomies										
Vaginal Repair and										
Hysterectomy	1	1	4	2		8				16
Hernia Repair			5	5	4	18				32
Nephrectomy				2	1	4				7
Cholecystectomy				1		2				4
Cesarean			9	4		1				14
Exploratory and										
Appendectomy				2		8		2		12
Extremity		1	1			3				5
Laminectomy and										
Spinal Fusion							4			7
Suprapubic Bladder				1		4				5
Transurethral and										
Rectal Prolapse				1	1	1	1			4
Total			1	2	22	21	6	107		167

TABLE 2.—Showing the duration of analgesia for various surgical procedures and the length of time between the start of operation and the need for supplement for pain.

Surgical Procedures	Duration Analgesia						Onset of Pain				
	Minutes	0	30	60	90	120	0	15	30	60	90
Pelvic Laparotomies	2	4	9	24	22	2	4	9	8		
Vaginal Repair and Hysterectomy	1	2	7	6						1	1
Hernia Repair	2	1	9	17	3	2	1		2		
Nephrectomy	3		4				1	2			
Cholecystectomy	1		2	1	1			1			
Cesarean		1	7	4	2			1	3		
Exploratory and Appendectomy	1	1	3	6	1	1	2			1	
Extremity			2	2	1						
Laminectomy and Spinal Fusion					7						
Suprapubic Bladder		1	3	1				2			
Transurethral and Rectal Prolapse		1	2	1				2			
Total		6	11	34	71	45	6	3	9	20	9

supplement of sodium pentobarbital or sodium pentothal intravenously to produce amnesia for the purpose of relieving nausea, apprehension or other of the unpleasant reactions sometimes observed in spinal analgesia.

Because of personnel shortages we found it impossible to check accurately the exact termination of the analgesia in many of those instances in which the anesthetic outlasted the surgical operation. In such cases we have considered the analgesia to have ended when the patient left the operating room. Actually, therefore, in those cases in which a supplement because of pain was not required, the effect of the anesthetic lasted an undetermined time longer than is indicated in Table 2. We were impressed with the fact that in the majority of cases effective analgesia lasted more than one and one-half hours, which compares favorably with that received from twice the dosage of pontocaine when ephedrine is omitted. If we may rightly assume that smaller doses of agent carry less hazard, then we must accept the conclusion that this technique will prove beneficial, for we are convinced that it is possible to secure satisfactory analgesia using these small doses in all types of operations in which a spinal anesthetic is commonly considered to be indicated.

An occasional delay in onset of analgesia has been noted and this may account for some of the cases in which results were listed as failures. However, one encounters a certain number of cases of delayed onset when using pontocaine and dextrose alone. In most instances satisfactory analgesia has been achieved by the time the patient is draped and ready for the surgeon to begin.

The incidence of severe hypotension is not significantly different than it is when only pontocaine and dextrose are used. In this series, 54 patients exhibited a variance of 40 or more mm. Hg. blood

pressure, but only a few of these showed a severe drop initially. It was observed that this variation in blood pressure occurred in the course of prolonged operations, following excessive traction and handling of the abdominal viscera and other shock inducing procedures. Potter and Whitacre<sup>6</sup> observed that little or no generalized systemic vasoconstriction resulted from intrathecal injection of ephedrine. Our experience substantiates this observation, since it was found necessary to inject ephedrine subcutaneously or intravenously in order to maintain satisfactory blood pressure levels. The effect of such vasoconstrictor agents was that which might be expected from the dosage given and showed no tendency to be influenced by any amount that was administered intrathecally.

Headaches occurred in 10 patients of this series. In two they were very mild and transient and in three others they lasted from one to three days. One of the patients had a headache before the operation. Only three of the patients presented the typical symptoms of post spinal anesthesia headache, and in them the headache terminated spontaneously within a few days. Nausea and vomiting occurred 13 times in the operating room and was observed three times postoperatively. We do not feel that the intrathecal administration of ephedrine has materially altered the incidence of the commonly seen complications of spinal analgesia. There was no instance in which a serious untoward reaction occurred. There were no deaths in the series.

#### SUMMARY

The intrathecal injection of ephedrine has been found to potentiate the effect of pontocaine-dextrose to the extent that doses of 5 to 8 mg. of pontocaine produce the same degree and duration of analgesia that may be expected from 12 to 16 mg. of that agent without the addition of the vasoconstrictor. This technique has been found to be useful in all types of operations in which spinal analgesia is the method of choice, including intra-abdominal operations.

The addition of 3 mg. of ephedrine to each milligram of pontocaine appears to be quite as effective as the ratio of five to one previously reported by other investigators, and might be expected to carry less hazard of undesirable ischemia of the cord and nerve roots.

In a reported series of 167 cases no serious complication was encountered and the incidence of minor undesirable reactions did not appear to be increased by this procedure. It is felt that the results of this comparatively small series are sufficiently encouraging to warrant further investigation and trial.

#### Discussion by CHARLES F. MCCUSKEY, M.D., Los Angeles

Dr. Martinson and Dr. Leffingwell have presented an interesting discussion of the use of vasoconstrictors intrathecally. Prolongation of anesthesia, in conjunction with a reduction of the dose of spinal anesthetic agent, should increase the safety factor.

The use of hyperbaric solutions of pontocaine and dextrose for upper abdominal procedures, when the height of anes-

thesia is obtained by tilting the head of the table downward, carries the more concentrated anesthetic solution to the upper levels rapidly. The tendency toward respiratory complications is thus greater than when an isobaric solution is used. When a vasoconstrictor is added to the intrathecal agent the onset of anesthesia is usually slower and the length of time required for the anesthetic agent to become fixed is increased. Following the injection of pontocaine it is ordinarily considered safe to place the patient in Trendelenburg position after 15 minutes. When ephedrine or other vasoconstrictors are added, this time should be increased by 10 minutes.

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## Inflammation as Considered by the Radiologist

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CELSUS (25 B.C.-45 A.D.) first stated our classic definition of inflammation in the following terms "Notae vero inflammationis sunt quatuor, rubor et tumor, cum calore et dolore." (Truly the signs of inflammation are four, redness and swelling with heat and pain.)

Since then the theories of what was happening in the body and in the tissues of an inflammatory process have changed with the passing centuries. It is the intention of this paper to bring up to date our thinking of what actually happens in inflammation and to correlate the experimental work in the use of x-ray in inflammation.

Inflammation may be broadly defined as the complex vascular lymphatic and local tissue reaction elicited in higher animals by the presence of micro-organisms or of non-viable irritants.

What happens in inflammation?

1. *Increased fluid passage through the capillary endothelial wall.* This seems primarily due to: (a) elevation in capillary pressure and (b) increased capillary permeability. The first is most likely due to a local axon reflex affecting the capillaries and the second to the liberation by injured tissue of the permeability factor termed leukotoxin.

Over 50 years ago Cohnheim<sup>3</sup> called attention to the increased permeability of minute vessels in an inflamed area. This early concept has been fully substantiated by the use of various techniques such as are involved, for instance, in studying the local accumulation within injured areas of intravenously injected dyes or finely divided material. Following injection trypan blue accumulates in the inflamed areas, staining them and demonstrating capillary permeability.<sup>14</sup>

Menkin<sup>15</sup> has conclusively shown that besides histamine, another substance which he calls leukotoxin is released in an inflamed area and increases capillary permeability. He has isolated this substance and definitely proved it to be separate from histamine. Local nervous reflexes probably play a role in modifying the initial development of the inflammatory reaction.<sup>16</sup> A transient increase in capillary pressure following the application of an irritant was apparently referable to a local axon reflex.

Krogh<sup>12</sup> noted marked capillary dilatation of mucous membranes that extended for a considerable distance beyond the irritant. When the irritant was applied after section and degeneration of the nerves, the affected capillaries became partially dilated over a localized area.

2. *Localization of the irritant.* The walling off of an inflamed area seems to be due to an enhanced passage of fibrinogen through the more permeable capillary wall. The draining lymphatics are blocked by thrombi and a fibrinous network. Various secondary factors such as presence of immune bodies in anaphylactic or allergic inflammation may reinforce the basic mechanism.

Menkin<sup>20</sup> has shown that *fixation* of powerfully necrotizing irritants such as *Staphylococcus aureus* occurs within two hours. Mild irritants, such as hemolytic streptococci, produce a delayed reaction, thus allowing relatively free penetration of the irritant into the circulation for a considerable period of time. Blockade of the draining lymphatics in such instances often takes place as late as two days following the introduction of the irritant.

3. *Migration of leukocytes.* The first cells to migrate into an inflamed area are polymorphonuclear leukocytes. This is related to the freeing of leukotoxin by the injured tissue. It contains factors concerned with both permeability and chemotaxis.

Menkin<sup>17</sup> has shown that leukotoxin is chemotactic both in the body and in the test tube.

The polymorphonuclear cells are gradually displaced by macrophages. The cell changes in acute inflammation seem to be conditioned by the pH of the exudate which in turn is often referable to disturbance in the local carbohydrate metabolism. The development of a local acidosis seems to injure the polymorphonuclear cells. Macrophages survive and predominate when the pH falls to the level of about 6.9 or 6.8. Further reduction in the pH kills all types of leukocytes and frank pus ensues.

Schade<sup>28</sup> reported that pus from acute abscesses had a pH ranging from 5.95 to 6.50; the pH of normal tissue fluid ranging from about pH 7.10 to pH 7.40. Menkin<sup>18</sup> injected turpentine in the pleural cavity and studied the pH and cellular response from day to day. As the inflammatory process progressed the pH changed from alkaline to acid. This usually occurred two to three days after injection of the irritant. Along with this decrease in pH there was a change in the differential leukocyte count. The percentage of polymorphonuclear cells fell, whereas the percentage of mononuclear phagocytes rose. The percentage of lymphocytes evidently plays no significant role in these cellular changes. The change in pH was shown to occur first. Menkin and Warner<sup>21</sup> showed that the pH was determined by the rate of lactic acid formation and the depletion of the alkali reserve at the site of injury.

With increase in the inflammatory reaction, there is a tendency for increased glycolytic activity as shown by a rise in lactic acid formation. This is ac-

Read before the Section on Radiology at the 76th Annual Session of the California Medical Association in Los Angeles, April 30-May 3, 1947.

accompanied by a fall in the  $\text{CO}_2$  capacity, and the pH correspondingly drops. A true lactic acidosis results at the site of the inflammation. (See Chart 1.)

#### *Effect of X-Ray on Normal Tissue.*

Wolfenden and Ross,<sup>32</sup> Wyckoff,<sup>33</sup> and many others<sup>23</sup> have experimentally shown that radiation in huge quantities (tens of thousands of roentgens) is bactericidal. These doses would produce untold damage if used on living human tissues.

Normal cells have a specific range of sensitivity.<sup>6</sup> By "specific range of sensitiveness" is meant that, when exposed to the same dose of rays under the same conditions, some kinds of cells are influenced more rapidly and to a greater degree than other kinds. At any particular time, however, all cells of one kind are not affected to the same degree by the same dose of rays. This is because the sensitiveness of different cells varies according to the phase of metabolism in which they happen to be at the time of irradiation. Cells that are actively dividing are more sensitive than those in the resting phase. Any factor which increases the rate of mitosis tends to increase the radiosensitivity of the cells. The sen-

sitivity of different kinds of cells is closely related to their degree of differentiation and to their life cycle.

The susceptibility of cells to radiation in order is as follows: (1) Lymphoid cells (lymphocytes in spleen, lymph nodes, intestinal lymph follicles, circulating blood, bone marrow, thymus, tonsil and other structures where these cells are present); (2) polymorphonuclear leukocytes in blood or tissue; (3) Epithelial cells (a) basal epithelium of certain secretory glands especially salivary; (b) basal epithelium (spermatogonial cells) of testis and follicular epithelium of ovary; (c) basal epithelium of skin, mucous membrane and certain organs such as the stomach and small intestines; (d) alveolar epithelium of lungs and of bile ducts; (e) epithelium of kidney tubules; (4) Endothelial cells of blood vessels, pleura and peritoneum; (5) Connective tissue cells; (6) Muscle cells; (7) Bone cells; (8) Fat cells; (9) Nerve cells.

#### *Other Responses:*

1. Vasodilatation occurs in tissue that has been irradiated with small doses of x-ray which begins in about six hours and lasts 24 to 48 hours. The effect

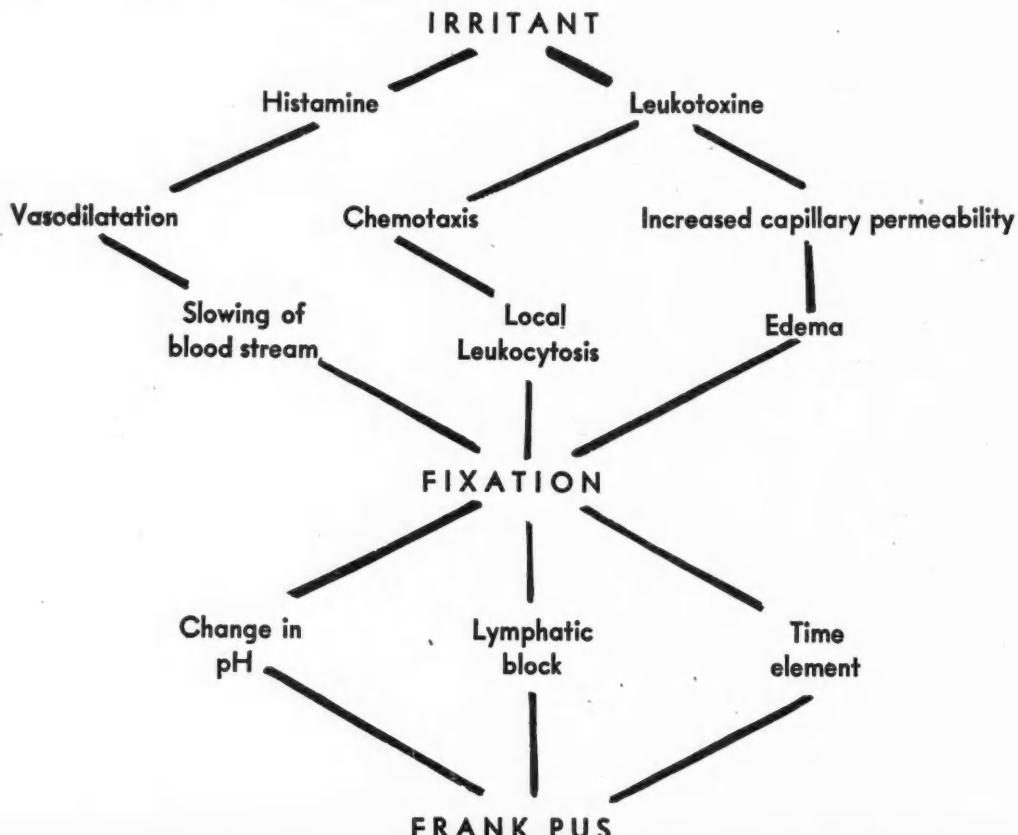


TABLE 1.—Diagram of the mechanism of the formation of pus in acute inflammation.

is more prompt with low voltage than with hard radiation. At no time have thrombi occurred such as Menkin describes in inflammations during fixation. The process has indicated an increase in the rate and quantity of blood flow through the irradiated area of the type seen in active hyperemia. Pendergrass, Hodes and Griffith<sup>24</sup> tested 84 subjects on the extensor surface of the forearm. A capillary count was done at 9 a.m. after injection of 1-1000 histamine, with further counts done at 4 p.m. and the next morning at 9 o'clock. The main factors used were 200 KV. 1/2 cu plus 1 al. filter. At 15 cm. distance 333 r were given in 3/4 minutes. A significant dilating effect on the skin capillaries was observed after six hours. This was largely gone after 24 hours. At 50 cm. distance, 301 r were given in 7.2 minutes. A distinct dilating effect was observed in 6 hours. This was still present after 24 hours. At 50 cm. distance, 308 r were given in 30.8 minutes. No significant change was seen in the skin capillaries in 6 hours and no definite effect was noticed in 24 hours. At 3 cm. distance 50 KV. was used and 300 r were given in one minute. A moderate capillary dilatation was noticed in six hours. This was increased and more marked in 24 hours.

2. Vohra<sup>31</sup> showed irradiation produces a change in the pH concentration of the cell plasma accompanied by increased permeability of the cell membrane. Other changes are decrease in cell respiration and increase of glycolysis. Inhibition of mitosis, production of mutations and death of rapidly dividing cells are, according to Vohra, the three main effects of small doses of radiation.

3. Tchaperoff<sup>30</sup> reports the inactivation of para-aminobenzoic acid by 50 r at 190 KV. This substance is important as a bacterial growth factor and is released by the tissues or synthesized in infections.

#### How X-Rays Affect Inflammation.

A. Active hyperemia in capillaries is induced by x-rays.<sup>24</sup>

B. The destruction of polymorphonuclear cells and lymphocytes releases proteolytic enzymes which dissolve dead tissue.<sup>22</sup> The lymph and blood channels are cleared of debris by the dual action of the radiation and the enzymes.

C. By changing the permeability, the hydrogen ion concentration and the carbohydrate metabolism of the injured cell and the surrounding cell plasma.<sup>31</sup>

D. By increasing the phagocytic ability of polymorphonuclear leukocytes and producing a generalized physicochemical change in the plasma which is antitoxic in nature. Crane<sup>6</sup> in 1907 showed that an increase in the opsonic index followed irradiation of infections. Hektoen<sup>10,11</sup> and other investigators<sup>4</sup> confirmed this. Glenn<sup>8</sup> showed the marked increase of phagocytic index against *Staphylococcus aureus* in rabbits produced 48 to 96 hours after irradiation with 100 r in air using 140 KV. Rosselet and Sarian<sup>26,27</sup> demonstrated this increased phagocytic activity by separating cells and plasma of irradiated blood. Irradiated leukocytes were then mixed with non-irradiated plasma and non-irradiated leukocytes

with irradiated plasma and tested for phagocytic power, using suspensions containing *Staphylococcus*. With the first mixture (i.e. irradiated leukocytes and non-irradiated plasma) no increase in phagocytic activity was noted, but with the non-irradiated leukocytes and irradiated plasma phagocytosis was definitely increased. They concluded that the result was due to some physicochemical change in the plasma. Bisgard, Hunt, Neely and Scott<sup>1</sup> definitely demonstrated an antitoxic factor present in the blood stream of rabbits 48 hours after irradiation of the abdomen. This substance, while not isolated, gave a 60 per cent survival rate to inoculated rabbits while all controls died. When the peritoneal washings of rabbits so treated were injected into the peritoneal cavity of stock rabbits, all survived while the controls died.

E. By destroying young fibroblasts. This occurs when larger total dosages are used and is more important in chronic inflammation and in scar formation. Doljanski, Goldhaber and Halberstaedter<sup>7</sup> showed that the immediate lethal dose of x-rays for rat sarcoma is the same as that for normal rat fibroblasts.

In the past 50 years practically all known inflammatory conditions have been treated with x-rays. Even before we knew the reason why, the beneficial effect in inflammatory processes was clinically demonstrated. The empirical use of x-rays in inflammation has been amply justified by both clinical and experimental studies over the years. In spite of the fact that x-ray therapy is non-specific and beneficial to all types of inflammation, if given in the proper dosage, the stage of development of the inflammation is very important. If irradiation in proper amounts is given before fixation (as described by Menkin), resolution will occur, if given after, pus formation is enhanced. The state of well-being of the body is very essential. In a debilitated individual, the response is much less than in a healthy organism.

The stage of an inflammatory process can be divided into acute, subacute and chronic for clinical purposes. Perhaps the acute and subacute stages would be divided by the occurrence of fixation in the tissues. The chronic stage most likely would be measured by the presence of fibroblast and lymphocytic infiltration.

#### CONCLUSION

Experimental evidence of how an inflammation occurs is presented. The experimental data of the effect of x-ray on an inflammatory process shows that: (1) An active hyperemia is produced; (2) White blood cells are destroyed; (3) The permeability, pH and carbohydrate and metabolism of the cell and plasma are changed; (4) Phagocytosis is increased and an antitoxic factor is formed in the plasma; (5) Fibroblasts are destroyed.

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## Laboratory Procedures in Diagnosis of Brucellosis

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EXCEPT for a positive culture of the infecting *Brucella* organism obtained from a suspected patient, there is no single completely reliable and satisfactory diagnostic procedure for brucellosis. However, since the disease is so bizarre and protean in its manifestations; since culturing the organism is rarely accomplished by the practitioner due to technical difficulties and to its slow growth; and since some reliable workers<sup>10</sup> estimate that less than 10 per cent of chronic brucellosis cases have an abrupt initial febrile onset such as occurs dramatically in the recognizable acute types of the disease, the diagnosis of brucellosis is based almost invariably upon laboratory procedures. The disease, furthermore, stands almost alone in the unanimity with which the above statement is supported by the medical profession, and in the knowledge that there are no pathognomonic findings in the chronic forms of human brucellosis.

When aliquot parts of the same patient's serum have been apportioned to 15 different laboratories of average standing, it has been common to secure 15 different results, varying from negative on the one extreme to positive in final dilutions as widely divergent as 1:40 to 1:1200.<sup>3</sup> There are many reasons for such variances, among which are unsuitable or isoagglutinating antigens and the recently demonstrated presence of "blocking antibodies" similar in mechanism to those described in Rh factor work.<sup>6</sup>

The identical techniques applied by Weiner and Race in their original work have revealed the masking effect of saline-suspended antigens, the phenomenon of dissociation of the blocking systems by serial dilutions (thus uncovering an "inhibiting zone" titer), the effect of heat on freshly drawn serums in potentiating agglutinations, and the enhancement of agglutinations by substitution of albumin for saline in antigen suspensions.

Neither bacteriologic antigens nor bacteriologic methods are universally standardized. It is suggested that if suitably located central testing laboratories were set up throughout the state with the cooperation of the various local health facilities and with the State Department of Public Health, these serious deficiencies might be largely corrected: (1) by using smooth-type sub-cultures under 48 hours old for antigenic material; (2) by testing at the same time against bovine, porcine, and caprine strains; and (3) by uniformly standardizing bacteriologic methods and materials, old and new. At these stations, special provisions for studies of brucella cultures might also be made. Adequately handled blood cultures repeatedly have been positive, not only in acute cases, but

also in afebrile chronic cases of many months' duration, a fact not generally known.

What constitutes a positive agglutination as conducted under the usual present conditions? No given numerical value: the widely held opinion that a positive agglutination titer of 1:80 is diagnostic is erroneous. Much more significant is a changing titer, repeated examination of the blood from the same individual at two-week intervals showing a titer which either rises or falls during the period of observation and is positive in a dilution of 1:80 or higher. Huddleston<sup>7</sup> reports 29 per cent of negative agglutinations in 100 bacteriologically proven cases due to *Br. abortus*. Dooley,<sup>2</sup> on the other hand, in 1932 studied 263 boys known to be ingesting raw milk from an infected herd which was concurrently responsible for two known clinical cases. They showed no manifestations of the disease whatever, yet 41 per cent of these boys had agglutination titers ranging from 1:40 to 1:1200 for brucella and 15 of these boys over prolonged periods of observation maintained titers of 1:320 and higher, but were asymptomatic.

Although this is not widely known, 90 per cent of service men vaccinated against cholera in the past war gave positive brucella agglutinations in titers as high as 1:1640.<sup>4</sup> Also, the opsonic index became strongly positive. Similarly, in approximately 11 per cent of cases, tularemia may give rise to false agglutinations for brucellosis.

Complement fixation has not been utilized to any degree in the laboratory diagnosis of brucellosis because it does not seem to be of value.<sup>8</sup> It has been attempted repeatedly in the study of animal brucellosis where no agglutination titers are present but where the disease is suspected. It is not technically as easy to perform as agglutination and repeated ambiguous results have been ascribed to theoretic anti-complement, to poor antibody formation, etc. As it appears to offer no advantage to the laboratory, its use has been circumscribed.

Reliance upon a positive skin test alone as diagnostic of existing active brucellosis is entirely erroneous.<sup>11</sup> Negative brucella skin tests in the presence of bacteremia have been reported frequently,<sup>9</sup> and, conversely, large numbers of people without clinical manifestations have been shown to have positive skin tests.

The danger of local tissue sloughing should be remembered when skin testing is done routinely and with large doses. Repeated skin testing with the vaccines commonly employed sometimes (but not invariably) causes significant agglutination titers to develop. Thus the effect of intradermal vaccines, used either as diagnostic tests or for therapeutic desensitization, may invalidate future aid from the laboratory.<sup>5</sup> This is more common than usually believed. It is

From the services of the Los Angeles County Hospital, Communicable Disease Division, and the Los Angeles County Health Department.

apparent that intradermal tests as at present widely used in diagnosis are of dubious value and widely abused in interpretation.

There exists in medical literature a philosophy that "brucella sensitization" may be a clinical entity.<sup>1</sup> Impressive data has been accumulated and interpreted in a manner which would tend significantly to correlate positive intradermal tests with psychoneurosis, allergy, and chronic arthritis. Such trends are to be evaluated with caution and deliberation, as they have appeared before in conjunction with other intradermal tests such as the tuberculin and coccidiomycin reactions. Undoubtedly, brucella sensitized individuals will be re-examined in the future with new diagnostic techniques and therapeutic methods, and it is probable that an accurate evaluation will clarify the issue. It is yet to be proven that the skin test is of greater significance relative to brucellosis than is the tuberculin skin test in relation to tuberculosis.

Similarly, the presence or absence of opsonophagocytic phenomena merely indicates: either (1) the presence of operative immunity (inasmuch as the phagocytes are seen to ingest living virulent organisms), or (2) a non-infected susceptible status (inasmuch as no phagocytosis occurs due to lack of the development of opsonins to stimulate ingestion of brucella organisms by the neutrophiles). Furthermore, the test is technically exacting and unless performed by well-qualified bacteriologists is seldom of any value. In any event, it does not prove active disease either present or absent.

From this discussion, it is apparent that aside from obtaining a positive culture of the organism, the diagnosis of brucellosis depends upon:

1. Evaluation of the epidemiological data when available.
2. Evaluation of clinical signs and symptoms.
3. Laboratory procedures comprehensive in scope, universally standardized, frequently repeated, technically dependable, and considered both in relationship to each other and to the clinical picture. Imperfect and unsatisfactory as laboratory tests appear to be at present, when properly evaluated they are the strongest available links in the chain of evidence leading to an acceptable diagnosis of human brucellosis.

The frontiers in medicine, both diagnostic and therapeutic, are continuously expanding. Diagnostically, the revelation of the blocking-antibody phenomena may add much to the clarification or

substantiation of difficult diagnoses. It has been recently demonstrated that egg-yolk embryo inoculations will support the growth of brucella organisms<sup>13</sup> and that this technique allows also for an *in vitro* test of the chemo-sensitivity of the organism recovered or cultured. Utilizing this technique, therapeutically, it has been demonstrated that the combination of streptomycin and sulfa drugs in adequate dosage provides a more consistently potent antidote to brucellosis than has hitherto been known. In the not infrequent instances where the last clinical resort of the physician is a "therapeutic trial" to combat the malady, this therapeutic combination may well confirm in retrospect a clinical diagnosis supported previously on the gossamer of controversial data.

The need for attempting to standardize and improve existing facilities for the diagnosis of brucellosis—a need that is urgent in view of the constantly increasing number of cases reported—is pointed out.

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## Influence of Mercurial Diuretics on the Excretion of Sodium, Potassium and Chlorides

DONALD E. GRIGGS, M.D., and VARNER J. JOHNS, M.D., *Los Angeles*

IT has been shown repeatedly that both mercurial diuretics and low sodium diets cause diuresis in patients with congestive heart failure, providing there is an adequate fluid intake. Most patients find a low sodium diet most unpalatable and many would prefer an occasional injection of a mercurial diuretic with less extreme sodium reduction in the diet. This study was undertaken to determine if possible the exact value of mercurial diuretics in augmenting or partially replacing the unpalatable extremely low sodium diets which have recently been used as an effective diuretic measure.

### METHOD OF STUDY

This is a report based upon the study of ten patients, nine of whom had congestive heart failure, and one of whom had portal cirrhosis. They were maintained on digitalis and were given no aminophyllin. Ammonium chloride was used in Cases Nos. 1, 3 and 9. All patients were maintained on a daily fluid intake of 3,000 cc. They were given diets containing one gram of sodium chloride daily except for Case No. 6 where the sodium chloride was raised during the course of the study to determine the effect of this increase in sodium intake upon its excretion. Urinary output was measured from 8:00 a.m. to 8:00 a.m. Two cc. (one cc. in Case No. 7) of a mercurial diuretic (mercuhydrin) was administered intravenously every third or fourth day. This was given at the beginning of the 24-hour period so that on the day of injection the mineral excretion was measured for the following 24-hour period.

Determinations of sodium and potassium were made by means of a flame photometer. This apparatus is similar to that described by Barnes et al<sup>1</sup> but the Beckman Spectrophotometer was used as a monochromator and light measuring instrument. Satisfactory concentrations were obtained by diluting the urine 1 to 50 with distilled water. The calibration was made by using standard sodium and potassium solutions containing 5 to 50 parts per million.

Chloride determinations were performed by direct potentiometric titration with silver nitrate using a National Tech. Lab. pH meter with silver and glass electrodes.

These determinations were done by Albert L. Chaney, Ph.D.

### REPORT OF CASES

CASE No. 1.—(Figure 1.) The patient received ammonium chloride 4 gm. per day during the entire period of observa-

tion. On the first three days he was digitalized and thereafter received only maintenance doses of digitalis. On the day before the first mercuhydrin injection was given, the total sodium excretion was greater than at any subsequent time. This was probably due to the fact that the patient was being digitalized at that time. Thereafter the total sodium excretion was greater in the 24-hour urine specimen after injection of the diuretic than on any of the other 24-hour urine specimens.

The percentage of sodium excretion or grams per liter was also increased in the 24-hour urine specimens following the mercurial diuretic.

CASE No. 2.—The patient was digitalized prior to hospital entry. When he entered the hospital there was evidence of digitalis intoxication with anorexia, nausea, vomiting and multiple ventricular premature contractions. These disappeared after six days, and digitalis therapy was resumed. Following the resumption of digitalis on the sixth day there was again noted an increase of total sodium excretion. Along with this increase of sodium excretion there was a corresponding increase of both the percentage and the total chloride excretion. With each injection there was a decrease of the percentage of potassium excretion, but due to the increased urinary output there was no corresponding decrease in the total potassium excreted.

CASE No. 3.—This patient received on the first day 1.2 mg. of digitoxin with no observed effect on the mineral excretion. The findings were essentially the same as in Case No. 2. On the days of the mercurial injection the percentages of sodium and chloride excretion were increased while the potassium excretion was decreased.

CASE No. 4.—This patient was on maintenance doses of digitalis before and during the study. The sodium and chloride excretion was increased on the days the mercurial was used. This was more marked with the first injection. As the patient depleted his reserves of body sodium by an output of sodium which exceeded the 1 gm. daily sodium chloride intake the total excretion of sodium became progressively lower. In spite of this the percentage of sodium and chloride continued to be higher on the days the diuretic was administered.

The output was not recorded on the last day that mercuhydrin was injected so we were unable to determine the total sodium output for that day.

CASE No. 5.—This patient was on maintenance doses of digitalis during the entire study, as he had been previously digitalized.

There was an increase in both the percentage and total excretion of sodium and chloride on the days of mercuhydrin injection but unlike the previous cases no material change in the potassium excretion was observed.

CASE No. 6.—(Figure 2.) This patient was on digitoxin 0.2 mg. daily during the entire study. Regardless of urinary output there was an increase in the percentage of sodium and chloride excretion on the days of mercuhydrin administration. The values for potassium were inconstant though

From the Department of Internal Medicine of the College of Medical Evangelists. This study was aided by a grant from the Lakeside Laboratories.

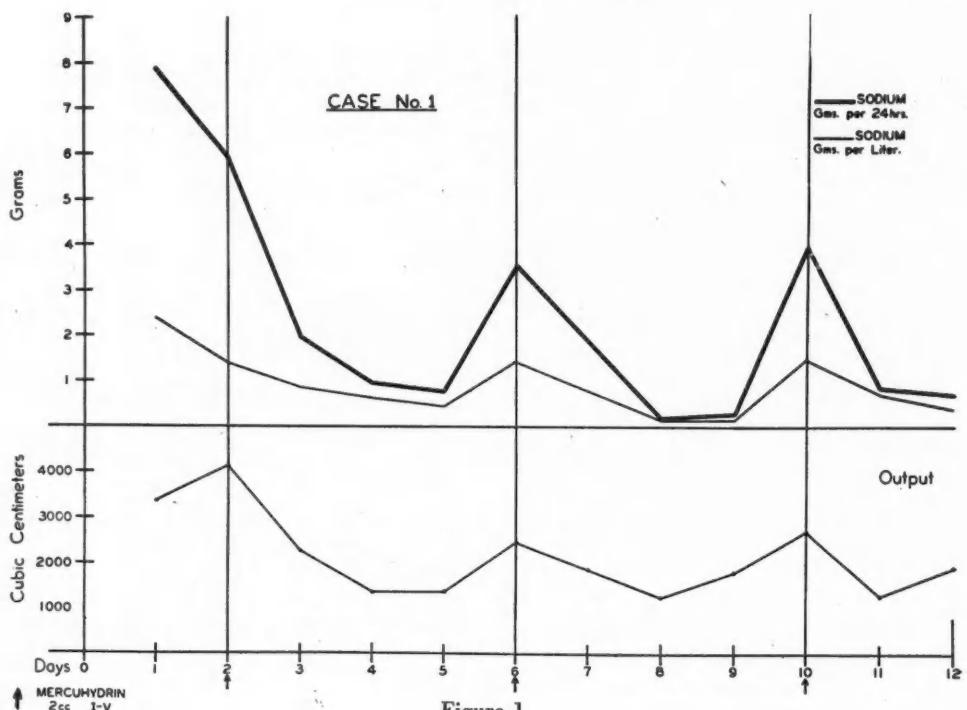


Figure 1

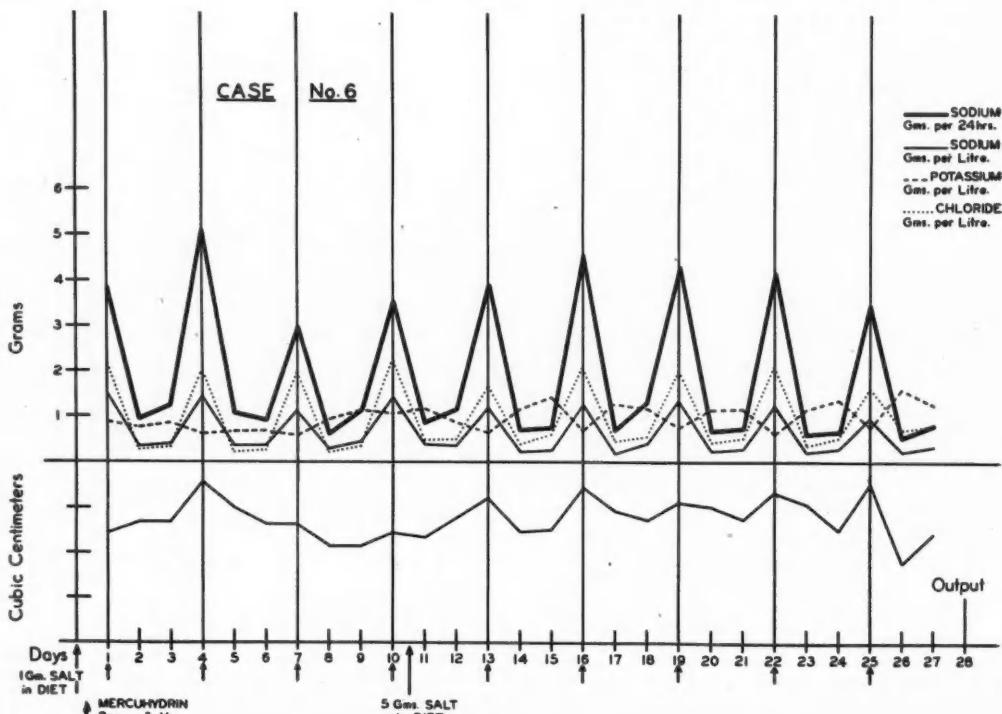


Figure 2

they tended to be lower on the days of the injection. On the eleventh day the sodium chloride intake was increased from 1 gm. to 5 gm. with no significant change in urinary output of sodium. In spite of the increase of sodium chloride intake he had no recurrence of signs or symptoms of congestive failure. This may be due to the fact that the sodium chloride excretion with the diuretics practically equalled this 5 gm. intake.

This patient had three thoracenteses, done on the first, tenth, and eighteenth days of our study. A total of 3,350 cc. of pleural fluid was removed. Only two specimens were analyzed for the sodium content of the pleural fluid. The first contained 2.85 gm. per liter and the second 4.5 gm. per liter. The pleural fluid had a higher sodium content than the average percentage in the urine so that this seems to be an important method of removing sodium from the body.

**CASE No. 7.**—(Figure 3.) This patient was digitalized with digitoxin during the first two days of our study. As with all the other cases more sodium was excreted on the days of mercurial injection than on the other days. The percentage of sodium was also greater. This case demonstrates the fact that as the sodium in the body is depleted the sodium excretion becomes progressively lower. This case also shows the amount of sodium excreted on six successive days without mercurial diuretics. In this patient only 1 cc. of mercuhydrin was administered every third day. While the urinary output in this patient was not large the total and percentage sodium excretion was almost as great as in the other patients who were given 2 cc. injections of mercuhydrin.

**CASE No. 8.**—This patient received ammonium chloride 4 gm. daily during the entire study. He was digitalized during the first three days of the study. The high sodium excretion on the second day may in part be due

to the digitalis. This case demonstrates again the decrease in sodium excretion as the sodium in the body is depleted by an excretion exceeding the 1 gm. daily sodium chloride intake.

**CASE No. 9.**—This patient was on maintenance doses of digitoxin. Ammonium chloride 4 gm. daily was given during the entire study. Following the first two mercurial injections the sodium excretion, both the percentage and the total, was greater than at any other time. This was not true of the third injection.

**CASE No. 10.**—This patient had portal cirrhosis with no evidence of congestive failure. The albumin globulin ratio was 3.6:3.0 gm. The 5 mg. bromsulphalein test showed a retention of 60 per cent after one-half hour and 35 per cent after one hour. The intravenous hippuric acid test showed an excretion of 0.16 gm. of benzoic acid in one hour. The non-protein nitrogen was 45. No digitalis or ammonium chloride was given. The sodium excretion was greater following the mercurial injections than at any other time. The total daily sodium excretion never exceeded 1 gm. even on the days the diuretic was given. The reason for this is not clear. This case is not included in the averages of the cases.

#### DISCUSSION

The average of the nine cases showed a sodium output of 0.81 gm. per liter on the days without the diuretic (Figure 4) and 1.96 gm. per liter on the days mercuhydrin was injected. The average total 24-hour output of sodium was 1.09 gm. on the days without injection and 4.83 gm. on the days of injection. This shows that the concentration of sodium in the urine was increased nearly two and one-half times

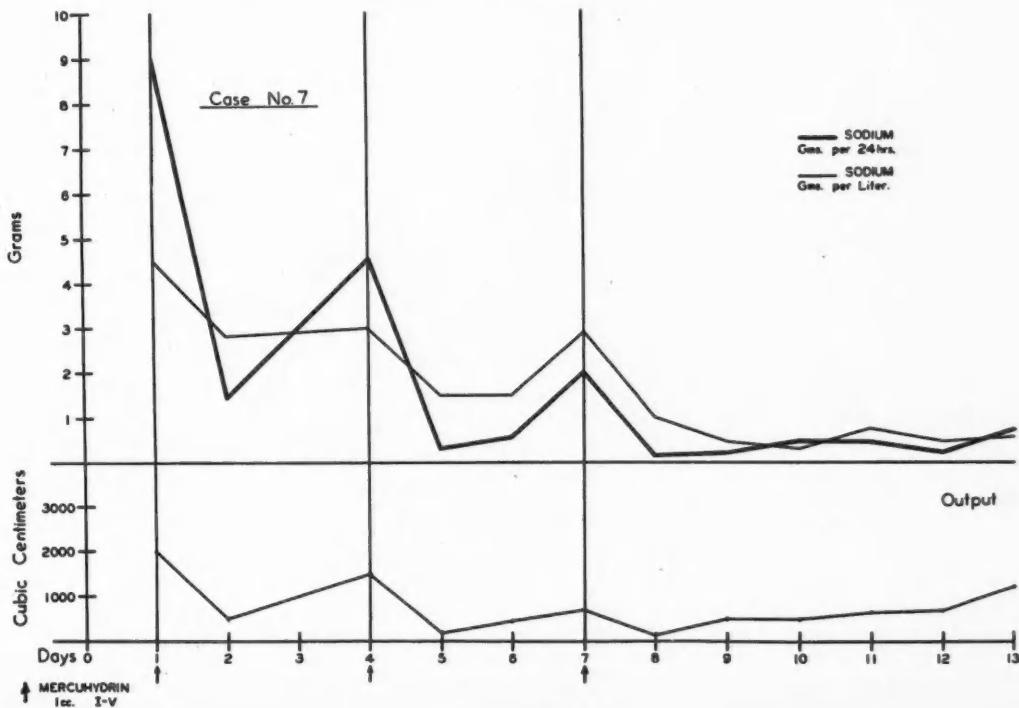


Figure 3

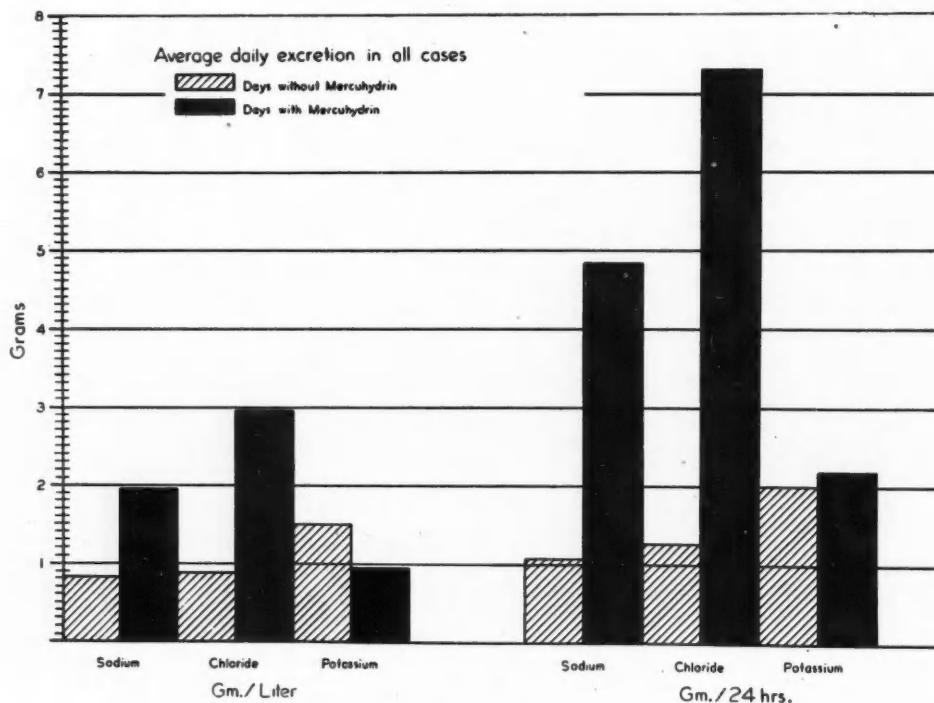


Figure 4

by the injection of the mercurial diuretic, while the average total excretion of sodium in 24 hours was increased more than four times by mercuhydrin injections. Reaser and Burch,<sup>5</sup> in an independent study, recently also found a marked increase both in the total and percentage sodium excretion after injections of a mercurial diuretic in a patient with congestive heart failure. They used a radioactive tracer  $\text{Na}^{22}$  to determine sodium excretion.

One gram of sodium (as we have measured it in the urine) is the equivalent of 2.54 gm. of sodium chloride which is the form in which dietary sodium is usually measured.

The average 24-hour excretion of 1.09 gm. of sodium on the days without injection is equivalent to 2.77 gm. of sodium chloride.

The average excretion of the 4.83 gm. of sodium for the 24 hours following the injection of mercuhydrin is equivalent to 12.27 gm. of sodium chloride or an increase of 9.5 gm. over the days the diuretic was not given. It would appear therefore from this small series that it may be possible by giving two injections of a mercurial diuretic weekly to increase the sodium chloride intake by 2.7 gm. per day. This would enable the patient to have a much more palatable diet without increasing sodium retention.

There was an actual decrease in the average percentage of potassium excreted in the urine following the injection of the mercurial diuretic. The average

potassium in grams per liter decreased from 1.51 to 0.9 following the injections. Due, however, to the diuresis on the days of mercurial injection the total excretion of potassium was slightly greater on those days—2.16 gm. in 24 hours as compared with 2.01 gm. in 24 hours. Melville and Stehle<sup>4</sup> also found that the potassium excretion following the injection of mercurial diuretics is less than the sodium excretion.

The average percentage chloride excretion following an injection of the mercurial diuretic increased more than three and one-half times, from 0.83 to 2.94 gm. per liter. The average total 24-hour excretion of chlorides increased sixfold, from 1.17 to 7.3 gm.

This increased urinary concentration of chlorides was noted by Hatzieganu, Gavrla and Borbil,<sup>3</sup> and Bouyoucos<sup>2</sup> and Stockton.<sup>6</sup>

#### SUMMARY AND CONCLUSION

1. In a study of nine patients with congestive heart failure who were maintained on a low sodium diet, the injection of 2 cc. of a mercurial diuretic, mercuhydrin, caused the following changes in the urine during the 24 hours after its injection:

(a) The average concentration of sodium in the urine was increased nearly two and a half times. The total sodium excretion was increased more than four times.

(b) The average concentration of potassium in the urine was decreased 40 per cent, although due

to the diuresis there was a slight increase in the total excretion of potassium.

(c) The average chloride concentration in the urine was increased more than three and a half times. The total chloride excretion was increased six times.

2. The average total sodium excretion after the administration of 2 cc. mercuhydrin was 4.81 gm. This is the equivalent of 12.3 gm. of sodium chloride, which is the form in which dietary sodium is usually measured. This is an increased excretion of 9.5 gm. of sodium chloride over the days on which the mercurial diuretic was not given.

3. It appears possible that for brief periods at least, the injection of mercurial diuretics will permit a more palatable, higher sodium chloride diet without any increase in sodium retention.

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# CASE REPORTS

- ◀ Parathyroid Carcinoma Causing Hyperparathyroidism
- ◀ Severe Stomatitis Due to Erythema Multiforme—Its Differentiation from Human Foot and Mouth Disease

## Parathyroid Carcinoma Causing Hyperparathyroidism

JUSTIN R. DORGELOH, M.D., *Oakland*

IN a review of the 322 cases of parathyroid adenoma reported up to 1945 it is stated that multiple tumors were described in 20 instances.<sup>2</sup> The reviewers point out, however, that only two of the 20 cases were reported after 1938, the year in which Albright's paper on secondary hyperplasia of the parathyroids appeared. Hence, it would appear that multiple true adenomas of the parathyroids are rare.

Malignant adenomas of the parathyroids causing *hyperparathyroidism* are considered very rare by most authors. Alexander<sup>1</sup> and his coworkers were able to find only seven reports of such cases in their review. These reviewers, however, appended reports of 14 new cases of hyperparathyroidism, with the opinion that the adenoma in 13 of the cases was malignant. Criteria of malignancy were invasion of capsule or blood vessels, or, in some cases, merely certain cytologic features. Metastasis was not demonstrated in any of the 13 cases, and in the seven reviewed reports metastasis was described in only one instance. It would seem that classification of parathyroid tumors as benign or malignant has depended largely on debatable criteria of malignancy.

### REPORT OF CASE

The patient, a 51-year-old Caucasian female, was first seen at St. Luke's Hospital in December, 1945. For two years she had experienced pain on movement of various joints. During the past year she had become very weak and had lost 24 pounds of weight. Vomiting had occurred during the last three months. Polyuria had been present for an unknown period of time. Incidental to an unrelated episode, asymptomatic calculi were demonstrated in the region of each kidney by roentgen examination in 1927.

Physical examination revealed a weak, ill woman with flaccid muscles. A mass was palpable in the region of the right lobe of the thyroid. The blood pressure was 142 mm. systolic and 82 mm. diastolic.

Laboratory studies demonstrated 10 gm. of hemoglobin per 100 cc. of blood, 3.8 million erythrocytes and 8,800 leukocytes per cubic mm. (the differential count of leukocytes was normal). The urine exhibited a specific gravity of 1.005. It contained 100 mg. of protein per 100 cc., and a large amount of calcium was demonstrated by the Sulkowitch test. Bence-Jones protein was not present. Microscopic examination revealed a few leukocytes and an occasional granular cast. Serum calcium was 18.5 mg., phosphorus 5.0 mg. per 100 cc. Alkaline phosphatase was 17.8 Bodansky units, acid phosphatase 1.5 units. Albumin was 3.4 gm., globulin 2.7 gm. per 100 cc. of serum. The non-protein nitrogen content was 54 mg. per 100 cc. of blood.

X-ray examination revealed generalized osteoporosis. In addition, there were cystic areas in ribs, cranium, vertebrae and long bones; some cystic lesions were apparently expansile. A rib fracture was demonstrated, as well as collapse of a vertebral body. Small calculi were seen in the region

of each kidney. Diffuse renal calcification was not demonstrable.

Sternal puncture and rib biopsy were carried out. Exploration of the neck was performed Dec. 31, 1945. Two tumors were found. The smaller was encapsulated and located a few millimeters from the inferior border of the right lobe of the thyroid, from which the tumor was distinct. The larger tumor was incorporated within the right lobe of the thyroid, and was thought to be a thyroid adenoma until rapid microscopic examination revealed its nature. Both tumors were extirpated.

On the day following operation the blood calcium had dropped to 11.0 mg. per 100 cc. of serum. On Jan. 3 the calcium level was 9.0 mg., numbness of the mouth developed, and Chvostek's sign could be elicited. Despite continuous calcium therapy, the blood calcium dropped to as low as 7.3 mg. The level then quickly became and remained normal. Postoperative Sulkowitch tests of the urine revealed no abnormal amount of calcium.

The patient then returned to her family physician in another city, where she improved and x-rays demonstrated complete healing of bone lesions. She returned to St. Luke's Hospital Feb. 18, 1947, because of recurrence of former symptoms. The calcium level was found to be 13.3 mg. per 100 cc. of serum, phosphorus 2.3 mg. Roentgen examination revealed demineralization of the calvarium, without cystic areas. The ribs appeared normal, a new cystic lesion of a tibia had appeared, and the renal calculi were still present. Studies were interrupted by departure of the patient for treatment elsewhere.

### TISSUE EXAMINATION

The rib biopsy specimen consisted of a little reddish tissue exhibiting no evidence of brownish color to gross examination. Microscopically, the typical picture of giant cell tumor was presented. Very little hemosiderin was apparent. The sternal puncture films contained very few cells other than non-nucleated erythrocytes. A few cells were relatively plump spindle-shaped forms with a vesicular, elongated nucleus. These conformed to the spindle cells found in sections of the giant cell tumor from the rib.

The smaller parathyroid tumor was 15x18x8 mm. in size. The smooth surface was completely encapsulated, and the bulging cut surface revealed a soft, tan, homogeneous tissue. The larger mass was 28x26x18 mm. in size, and was encapsulated except over a small area where it had been fused to a little thyroid tissue. Sections revealed a pinkish-gray tissue traversed by narrow and broad bands of firm white tissue.

Microscopically, the two tumors were similar. They were undoubtedly of parathyroid origin. There were masses and anastomosing columns of large polygonal and columnar cells (see Figures 1 and 2). Most of the cells were of the "chief cell" variety, with foamy cytoplasm. A moderate number were of "water clear" type, and a few oxyphil cells were present. The cells were much larger than normal, and many presented a very large nucleus with one or two very prominent nucleoli. An occasional mitotic figure was seen. The stroma was scant, save for areas of fibrosis in the larger tumor. The

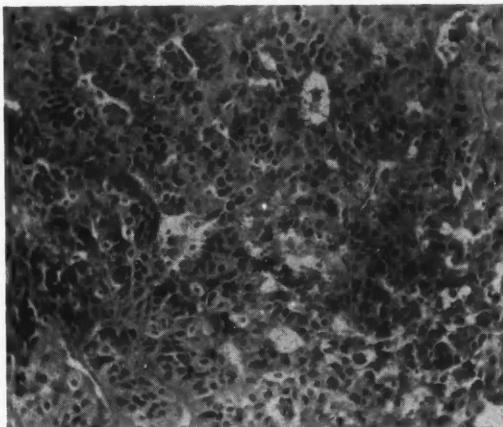


Figure 1.—Magnified 130 times.

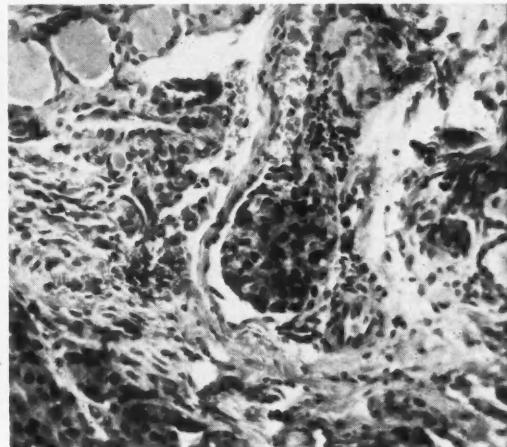


Figure 3.—Magnified 160 times.

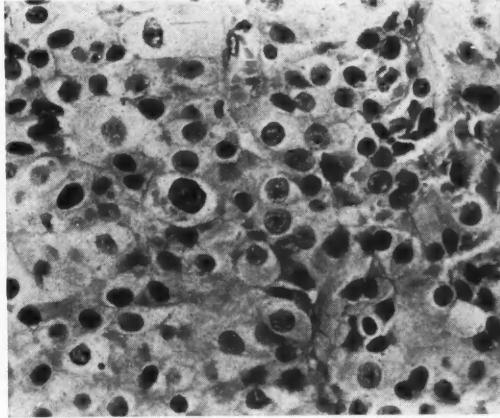


Figure 2.—Magnified 440 times.

latter tumor presented invasion of thyroid tissue and growth into the lumen of venules (see Figure 3). A small separate fragment of tissue removed during the surgical operation consisted of apparently normal thymic tissue enclosing a small amount of parathyroid tissue; the latter appeared normal.

#### ANIMAL INOCULATION

Extracts\* of each tumor were injected intravenously into rabbits. The calcium level of each animal rose to an average value of 19 mg. per 100 cc. of serum, from a pre-injection level of 12 mg. The experiment was controlled by injection of other rabbits with various tissues.

#### DISCUSSION

The histologic features of the parathyroid tumors in the case reported were those commonly accepted as being indicative of malignancy. In view, however, of the fact that only one case of metastasis from a malignant adenoma of the parathyroid with hyperparathyroidism has been reported, a circumspect attitude in the diagnosis of "malignancy" would seem desirable. One might consider, in the present case, that the tumors represent multicentric origin or, on the

other hand, malignant extension. According to either interpretation, this case presents a rare situation. Investigation of the recurrence of hyperparathyroidism in the patient was aborted by her decision to seek treatment elsewhere. A preliminary part of the investigation was to have been biopsy of the new tibial lesion to determine if it represented metastasis of parathyroid tissue, or merely another giant cell tumor.

#### SUMMARY

Extrication of two parathyroid tumors was followed by temporary disappearance of hypercalcemia and bone lesions. Extracts of the tumors produced hypercalcemia in animals. The tissue findings are discussed, particularly in regard to possible malignancy of the adenomas.

Note: The author is indebted to the patient's physicians, Dr. P. A. Taylor and Dr. A. R. Kilgore, for permission to present the pathologic features of this case.

\* \* \*

*Addendum:* The above paper is reproduced as presented before the pathology section of the California Medical Association under the title "Hyperparathyroidism, Report of a Case Presenting Two Parathyroid Adenomas, Possibly Malignant." Subsequently it was learned that later in May, 1947, operation at the Mayo Clinic revealed local recurrence of tumor and metastases to right lower deep jugular lymph nodes. In both locations the tumor was identical in microscopic appearance to that found at the original operation. The blood calcium level was 17 mg. per cent just before the second operation, then fell to normal postoperatively. The case is still under investigation.

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#### Discussion by E. M. HALL, M.D.

I concur in the diagnosis of "malignant adenoma of the parathyroid" as presented by Dr. Dorgeloh. Well-substantiated malignancies of the parathyroid glands are rare, but this invades the thyroid gland and at least one of the blood vessels, thus setting the stage for metastasis.

A similar tumor was reported by Hall and Chaffin in 1934. A 46-year-old white male had a mass the size of his fist removed from the left side of his neck in March, 1931. The mass was of liver-like consistency except for one part that was cystic. The diagnosis made by another pathologist was "adenoma of the parathyroid and cyst adenoma of the

\* Method of Collip, as described in *Physiol. Basis of Med. Pract.*, Best & Taylor, 3rd ed., p. 1185.

thyroid gland." The blood calcium was 9.9 mg. per cent and no changes were demonstrated in the bones by x-ray examination. The patient returned to the hospital in November, 1932, with several small recurrent nodules in or near the operative scar. They ranged from 1 to 1.5 cm. in diameter, some of them definitely invading muscle. Microscopic examination revealed not only invasion of skeletal muscle but also a mass of tumor cells within a small blood vessel in the fibrous capsule. Blood calcium and phosphorus determinations were within normal limits. The bones appeared normal in the roentgenogram. The patient was able to return to work and remained well until late in December, 1936. Weakness, night sweats and loss of weight disturbed him during the early weeks of 1937. He developed fever and pain in the chest, and pneumonia was diagnosed. The fever and pain lasted for some three months. By September, when the patient entered the Los Angeles County General Hospital, he had lost 50 pounds in weight. Roentgen examination showed the right lung field almost completely filled with a hazy homogeneous density.

The patient died in September, 1938. At autopsy massive tumor metastases were shown to have replaced most of the right lung, and a 3 cm. nodule was present in the lymph

nodes at the hilum. Microscopic examination revealed a picture very similar to the tumor seen previously. Here, then, is an instance in which neoplasm similar in cell pattern and in invasive properties to the one reported by Dr. Dorgeloh, finally produced metastases to the lung with fatal outcome. It was four years from the time of the second operation to the onset of symptoms.

It is interesting that bony changes including cystic areas and benign giant cell tumors were present in Dr. Dorgeloh's patient. Of the 20 parathyroid malignancies reported to 1940 only about one in four revealed bone destruction and high serum calcium levels. In a recent report by Alexander, Broders, et al (1944) 12 out of 13 adenomas of the parathyroids reported were considered Grade I adenocarcinomas. It is evident that a less rigid standard is used in classifying this group since malignancy was judged on a basis of cellular anaplasia while no invasion of surrounding tissues or blood vessels was present except in one case.

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## Severe Stomatitis Due to Erythema Multiforme — Its Differentiation from Human Foot and Mouth Disease

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BECAUSE of its varied and protean clinical manifestations, erythema multiforme is of general medical interest. The disease was first recognized in 1817 by Bateman and Bulkley, in 1846, reported the first American cases as "Herpes Iris." Hebra,<sup>3</sup> in 1866, fully described the morphologic features of the eruption under the term "erythema exsudativum multiforme." Hebra was among the first investigators to recognize erythema multiforme to be of internal or systemic origin and not local in causation. Quinquaud ranks priority in describing the mouth lesions in vesiculobullous erythema multiforme. The implication of the viscera in the etiology of erythema multiforme was stressed at the beginning of this century by Osler,<sup>8</sup> who called the internal features of the disease to the attention of the medical world.

Erythema multiforme (Hebra) is essentially cutaneous in location and oral mucosal involvement is present in about 25 per cent of the cases. Rarely, the mucosae of the eyes, nose, esophagus, labia minora, preputium, glans penis, urethra, vaginal tract, cervix and anus are involved.

The association in erythema multiforme, however, of severe vesiculobullous oral mucosal lesions with a paucity of cutaneous lesions has produced confusing and bizarre clinical pictures. In some instances, severe mucous membrane involvement has occurred with entire absence of a skin eruption.<sup>1</sup> Some investigators have described these unusual mucous membrane manifestations of erythema multiforme as new diseases. Thus Rendu, in 1916, termed a severe bullous stomatitis associated with similar lesions on the conjunctival, anal, and penile mucous membranes and a cutaneous vesicular eruption, "Ectodermose Erosive Pluri-

officielle." Baader, in 1925, named severe erythema multiforme of the oral cavity associated with cutaneous lesions, "Dermatostomatitis." Stevens and Johnson,<sup>10</sup> in 1922, reported erythema multiforme with predominant involvement of the oral and conjunctival mucous membranes as "a new eruptive fever associated with stomatitis and ophthalmia." This syndrome has also been referred to in the medical literature as "Stevens-Johnson disease." In the erythema multiforme group may also belong the "triple syndrome complex" of Behcet consisting of ulcerations of the oral and genital mucous membranes associated with retinitis and iridocyclitis.

When erythema multiforme is associated with stomatitis, fever, malaise and vesicular lesions on the hands and feet, a clinical picture is produced that resembles foot and mouth disease in man. If this clinical picture occurs in a resident of a dairying or livestock-raising area such as California, where foot and mouth disease epidemics in animals occurred in 1914, 1924, and 1929,<sup>7</sup> it can easily lead to an unwarranted diagnosis of the human form of foot and mouth disease when the clinical diagnosis is unsupported by confirmatory laboratory tests. This close clinical resemblance between erythema multiforme and the human form of foot and mouth disease has been stressed by Klauder<sup>4</sup> and Lever. Internists, pediatricians, ophthalmologists, and dermatologists may especially be called in consultation in cases of erythema multiforme, the choice of consultant depending on the location of the mucous membranes attacked and the constitutional or systemic manifestations predominant. It is the purpose of this article to report a case of severe stomatitis due to erythema multiforme resembling the human form of foot and mouth disease and to differentiate this type of stomatitis from important simulating mouth eruptions.

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## REPORT OF A CASE

The patient, a school girl, aged 15, presented a sore, swollen mouth, malaise, prostration, and fever of 11 days' duration. The mouth eruption began with a painful red spot on the right inner cheek. Blisters and redness soon appeared and spread to involve the tongue, cheeks, throat, and lips. The mouth and throat became so painful and swollen that the patient had difficulty in eating, swallowing, and speaking. Salivation was profuse. The daily temperature had ranged from 99.5° F. to 102° F. since the onset of the illness. About one week after the onset of the stomatitis, red spots and small blisters appeared on the palms, backs of the hands, and the plantar surfaces of the feet. No subjective symptoms were associated with the skin lesions. There was no history of mouth eruption, drug ingestion, or the use of mouthwashes or new dentifrices preceding the onset of the present illness. No other members of the family had suffered from a similar disorder.

**Examination.** The girl appeared acutely ill and had difficulty in opening her mouth, swallowing, and talking. The breath was fetid. The temperature was 101° F. and the pulse rate 82. Heart, lungs, and abdomen were normal to physical examination. Examination of the mouth and throat showed the mucosae of the lips, cheeks, tongue, hard and soft palate, gums, and throat to be intensely red, swollen and eroded. White denuded hemorrhagic shreds of mucosae were scattered throughout the oral and pharyngeal cavities. A few small vesicles were seen on the hard and soft palates, buccal mucosae, and ventral surface of the tongue. Lymphadenopathy was present in the cervical and sublingual regions. Small macules and vesicles were scattered over the face, palms, dorsa of the hands, fingertips, and plantar surfaces of the feet. Because of previous animal foot and mouth disease epidemics in California, the human form of foot and mouth disease was considered in diagnosis. There was no history of exposure to this infection. Veterinarians informed us that there were no recent reports of the disease in animals in California or nearby areas. Laboratory tests for this disease were nevertheless included in our examination to definitely rule out the possibility of human foot and mouth disease because of the confusing clinical picture.

**Laboratory Examinations.** Smears from the oral cavity lesions were negative for the presence of Vincent's organisms. Cultures from the mouth and throat grew *staphylococcus aureus* and *streptococcus viridans*. Inoculation of a guinea pig's scarified pads with contents of vesicles (Waldmann and Pape's method) was reported negative for the virus of foot and mouth disease by state and federal veterinarians. Blood cultures were negative and the results of the blood count and urine examination were normal. Inoculation of oropharyngeal swabbings and serum from mouth vesicles onto the scarified cornea of a rabbit was negative for the presence of the virus of herpes simplex. The diagnosis was severe stomatitis due to erythema multiforme (Hebra).

**Treatment** was symptomatic. Soothing alkaline mouth-washes and nicotinic acid (150 mg. daily) were prescribed. Calcium gluconate, 1.0 gr. (1½ grains), was administered intravenously daily. The cutaneous eruption was treated with a soothing calamine shake-lotion.

**Course.** Twenty-four hours following initiation of treatment the mouth eruption was much improved. The oral swelling and pain had subsided and she was able to open her mouth, chew food, and swallow with less difficulty. The cutaneous eruption, however, had increased in intensity and spread to involve the extensors of the forearms. The patient complained of tenderness of the fingertips, where there were vesicular lesions. During the following ten days the stomatitis and cutaneous eruption gradually subsided and disappeared without leaving residual secondary lesions. The



Figure 1.—Severe stomatitis due to erythema multiforme resembling the human form of foot and mouth disease showing swollen lips with erosions.

temperature slowly became normal in one week. No recurrence of the stomatitis or cutaneous eruption appeared during the ensuing year while the patient was under observation.

## COMMENT

The diagnosis of typical erythema multiforme (Hebra) is not difficult. There is usually a history of seasonal occurrence (spring and fall), provocation of the dermatosis by sunlight, and a tendency of the disease to relapse and recur. The lesions are essentially cutaneous, bilateral, bluish-red, and have a predilection for the face, lateral aspects of the neck, extensor surface of the forearms, and dorsa of the hands and feet. The eruption is commonly erythematopapular or vesiculobullous, and oral lesions, when present, are usually of mild or moderate intensity. Due to the loose structure of the oral mucous membranes and lack of epidermal cohesion, vesicles or bullae in the mouth are rarely found intact, as they break down into superficial erosions. The clinical course of erythema multiforme (Hebra) is usually mild and the patient may suffer from slight malaise, fever, and rheumatoid articular pains. The duration of the disease averages two to six weeks and lesions disappear without sequelae.

Because of simulation of a host of other afflictions, atypical erythema multiforme primarily attacking the oral mucosae, as in the reported case, may present the greatest difficulties in diagnosis. An aid to the recognition of this type of severe stomatitis may be had by differentiating two important factors that can produce severe erythema multiforme-like simulating manifestations in the mouth and skin—drugs and infection. The ingestion of such drugs as phenolphthalein, antipyrine, barbiturates, and sulfonamides, by susceptible individuals can produce vesiculobullous erythema multiforme-like manifestations of the oral cavity and integument. Rarely, drugs may attack the mouth mucosae without signs of skin involvement and produce a severe stomatitis that may be very difficult to diagnose. Stomatitis due to drugs may also be confusing because of associated fever and



Figure 2.—Severe stomatitis due to erythema multiforme resembling the human form of foot and mouth disease showing involvement of the oral cavity and lips.

constitutional symptoms. In drug stomatitis, however, there is often a history of drug ingestion or sensitivity and an exanthem may show morphologic characteristics of the causative drug. If, however, the drug exanthem is erythema multiforme-like in location and appearance, clinical differentiation between drug sensitivity and erythema multiforme (Hebra) may be impossible and the diagnosis must be deferred until more revealing signs appear.

Among infectious diseases reported to produce the erythema multiforme-like symptom-complex are typhoid fever, streptococcal septicemia, and typhus. Severe stomatitis, however, is rarely associated with these infections and specific diagnostic laboratory examinations (Widal test, blood cultures, Weil-Felix reaction) are of aid in differentiation.

Erythema multiforme of the Hebra type, as illustrated by the reported case, is of unknown origin and is classified as "idiopathic." Some "idiopathic" examples of the disease, however, have been reported to be associated with foci of infection, such as abscessed teeth, or the herpes simplex virus. Keil has summed up the present state of our knowledge of the origin of erythema multiforme (Hebra) by stating that "the etiologic factor or factors in erythema multiforme exsudativum remain to be discovered."

The transmission of the virus of foot and mouth disease to man is rare. Tautwein, in 1932, listed only three cases of human foot and mouth disease in humans that were proven by transfer of the bleb content to susceptible animals. Meyer<sup>6</sup> has pointed out that invariably, during an epidemic of foot and mouth disease in animals, physicians report that they have seen the same infection in man. When careful inquiries are made, however, no conclusive proof is obtainable that the virus of foot and mouth disease was responsible for these reported cases. Meyer states that since a differential diagnosis cannot be made on clinical grounds, the reports of many exanthemata diagnosed as foot and mouth disease without an infection or cross-immunity test are of

little value. It is our belief that acute febrile vesiculobullous stomatitis associated with vesicular lesions on the hands and feet, which is confused with human foot and mouth disease, is usually due to erythema multiforme or aphthous stomatitis (herpetic fever).

Ultimate differentiation between severe stomatitis due to erythema multiforme and stomatitis due to the human form of foot and mouth disease is accomplished by means of laboratory procedure. Clinically, the two diseases may be indistinguishable one from the other, inasmuch as the erythema multiforme-like picture may be produced by the filtrable virus of foot and mouth disease. Even tenderness of the finger tips, with vesicular lesions, and limitation of the eruption to mucocutaneous junctions and fingers and toes, as stressed by Sutton, may be present in erythema multiforme and lead to confusion. The virus of foot and mouth disease is found in the vesicle fluid of the lesions and the diagnostic standard laboratory test consists of inoculation of the vesicle fluid in the scarified pads or volar skin of a guinea pig. Positive reaction to the inoculation is appearance of suppurative blebs on the pads in 24 to 48 hours, with eventual extension of the disease to the guinea pig's tongue, lips and palate. Sutton has pointed out that this laboratory test may be performed only by state or federal veterinarians by special permission of the United States Bureau of Animal Husbandry. The nature of the virus also may be demonstrated by cross-immunity tests. Fessler<sup>2</sup> and Richter<sup>9</sup> have outlined the methods which must be chosen to prove the existence of foot and mouth disease virus in the lesions in humans. The importance of the final laboratory infection test was illustrated in the case of our patient, in whom, clinically, the stomatitis and cutaneous eruption due to erythema multiforme was indistinguishable from the human form of foot and mouth disease.

Other types of stomatitis that must be differentiated from stomatitis due to erythema multiforme are stomatitis due to Vincent's infection, aphthous infection, dystrophic epidermolysis bullosa, contact irritants (stomatitis venenata), and pemphigus. Erosive painful stomatitis due to infection by Vincent's fusospirochetal organisms can usually be diagnosed by typical localization of the lesions in the mouth (tonsils and gingivae) and smear examinations. Keil, however, has pointed out that stomatitis due to erythema multiforme as well as other oral diseases may give a positive smear for Vincent's disease. Fusospirochetal infection is rarely accompanied by an exanthem and the presence of skin lesions associated with a vesiculobullous erosive stomatitis would tend to exclude the diagnosis of fusospirochetal disease. Therapeutic tests may also aid in the diagnosis of Vincent's infection by the known response of fusospirochetal organisms to oxidizing agents, arsphenamines, and penicillin and the failure of erythema multiforme stomatitis to respond to any specific medication.

The differentiation of aphthous stomatitis due to the herpes simplex virus usually offers little difficulty. Aphthous or herpetic stomatitis is characterized by frequent occurrence in children, discrete papulovesicles that breakdown into painful ulcerations surrounded by an inflammatory halo and a predilection of the lesions for the buccal mucosa, lips, and edges of the tongue. A vesicular generalized exanthem with lesions on the fingers and toes associated with aphthous stomatitis has been reported by Mayer. Inoculation of vesicle fluid or swabblings from the mouth lesions in aphthous stomatitis onto the scarified cornea of a rabbit will prove the presence of the virus of herpes simplex. Typical herpetic vesicles develop within 24 to 48 hours, and this is followed by a purulent keratoconjunctivitis.

Ten cases of aphthous stomatitis simulating human foot and mouth disease were reported by Lebailly in 1921. The differential diagnosis in Lebailly's cases was established by

negative reaction in an attempt to inoculate cattle with vesicle fluid of the mouth lesions. Dystrophic epidermolysis bullosa may cause erosive oral cavity lesions simulating stomatitis due to erythema multiforme. The differential diagnosis, however, is not difficult, as dystrophic epidermolysis bullosa occurs in early childhood, is familial in occurrence, and is associated with cutaneous lesions due to mechanical trauma at sites of pressure. Characteristic atrophy and scarring occur at the site of healed lesions in the oral cavity and skin in this disease and are absent in erythema multiforme.

Chemical irritants may produce vesiculobullous and erosive stomatitis venenata. These irritants can be found in dentifrices, dentures, and mouthwashes. The history of use of mouth irritants, performance of patch tests with offending substances, lack of constitutional symptoms, and the absence of an erythema multiforme exanthem will aid in the differentiation.

In the early stages of an erosive bullous stomatitis, before the appearance of an exanthem, pemphigus and erythema multiforme may be impossible to differentiate clinically. The course of the disease, the appearance of typical erythema multiforme skin lesions with absence of "Nikolski's sign" in the skin, and a negative phytotoxic test (Pels-Macht) would aid in excluding pemphigus in the differential diagnosis. At times, however, the differentiation of stomatitis caused by these two diseases is very difficult, if not impossible, and can only be made after prolonged observation of a particular case.

The treatment of stomatitis due to erythema multiforme is symptomatic. Inasmuch as the cause of the disease is unknown, medicaments recommended in its treatment are employed empirically. The value of epinephrine, salicylates, alkalinization, calcium, sulfanilamide and local topical applications<sup>5</sup> in erythema multiforme is disputable. The favorable reports found in the medical literature of response of the disease after the use of these agents cannot be evaluated without controls, as erythema multiforme is a self-limited eruption.

The prognosis of severe stomatitis due to erythema multiforme varies according to the complications that may appear due to spread of the disease from the oral cavity into the larynx, tracheobronchial tract, lungs, and esophagus. Fatalities have been reported in severe cases due to bronchopneumonia secondary to tracheobronchial tract involvement. Uncomplicated erythema multiforme stomatitis is a self-limited disease that usually clears in two to four weeks without sequelae. Recurrence of seasonal type and relapse, however, is a frequent and characteristic finding in erythema multiforme and prognosis as to absolute cure in any particular attack of the disease involving the oral cavity or skin must be guarded.

#### SUMMARY AND CONCLUSIONS

A case of severe stomatitis due to erythema multiforme resembling the human form of foot and mouth disease is reported.

Severe stomatitis due to erythema multiforme produces a clinical picture that may lead to confusing it with the human form of foot and mouth disease unless standard diagnostic laboratory procedures of infection and cross-immunity tests are performed. Proven cases of the human form of foot and mouth disease are rare and physicians should be cautious in making this diagnosis without laboratory proof in a patient suffering from severe febrile vesiculobullous stomatitis associated with vesicular lesions on the hands and feet.

Other forms of stomatitis differentiated from stomatitis due to erythema multiforme are those due to drugs, Vincent's disease, aphthae, dystrophic epidermolysis bullosa, contact irritants (stomatitis venenata), and pemphigus.



Vesicular lesions of erythema multiforme on the hand resembling the human form of foot and mouth disease.

The varied mucosal and constitutional manifestations of erythema multiforme have produced unusual clinical pictures that have been described as "new diseases" in the medical literature. To avoid confusion, these so-called new diseases should be recognized and properly classified as atypical erythema multiforme.

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## CLINICAL SYMPOSIUM

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### Palliative Management of Mammary Carcinoma

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**S**URGICAL literature on mammary carcinoma is so largely concerned with the radical, curative approach to the disease that one is apt to forget that half or more of all women with this neoplasm are incurable when first examined. Further, there are certain forms of breast cancer which are technically operable but biologically incurable, and in which radical mastectomy may be harmful. The palliative management of this neoplasm is, therefore, as important statistically as the surgeon's attack on the potentially curable lesions.

The palliative results achievable in cancer of the breast are frequently impressive, for women can live with the disease effectively controlled for five to ten years or longer and continue to be socially and economically useful members of society. Not infrequently such prolongation of life is of immense importance to the family unit with young children. With an estimated 70,000 current cases of breast cancer in the United States, the clinical management of these patients is a recurring problem in general practice. The cooperation of physician, radiation therapist and, less often, the surgeon constitutes the desirable liaison in this problem.

#### CRITERIA OF INCURABILITY

Of first importance in establishing indications for palliative management are the criteria which determine incurability. Essentially, these criteria are those which make the patient ineligible for radical mastectomy, and are based either on the stage of the disease or its pattern of growth, as follows:

- (A) A far advanced primary lesion in the breast.
- (B) Extensive regional metastases.
- (C) Distant metastases.
- (D) Evidence of a highly malignant, rapidly growing, biologically incurable lesion.

Reducing these basic factors to specific situations, an arbitrary outline by which one may determine incurability can be offered.

#### DETERMINING FACTORS

##### (A) EXTENT OF PRIMARY LESION

1. *Extensive skin involvement.* Minimum skin attachment or retraction may be due to a scirrhus, superficially located tumor with dermal or subdermal sclerosis. Actual skin involvement means extensive permeation of local lymphatics and is as grave an omen as supraclavicular nodal metastases. "Peau d'orange" is a sign of late cancer. Satellite nodules in adjacent skin are a particularly bad sign.

2. *Fixation to pectoral fascia or chest wall.* Also a sign of late cancer, for if the disease has reached the pectoral fascia it is also in the subpectoral lymphatics and thus beyond the deepest plane of chest wall dissection in radical mastectomy.

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3. *Ulceration of skin.* Full thickness ulceration of any extent is usually a sign of inoperability, except in some slowly growing lesions without evidence of regional nodal metastases. In elderly women even with extensive ulceration the breast may be fully mobile and the regional nodes clear.

4. *Extension beyond the midline.* Occasional inner quadrant lesions near the medial periphery of the breast will have infiltrated across the midline, thus gaining access to the lymphatic system of the contralateral breast and axilla. This is an added hazard with inner quadrant lesions which frequently metastasize in the region of the internal mammary circulation.

##### (B) EXTENSIVE REGIONAL METASTASES

"Regional" lymph nodes include axillary and infra-clavicular groups. Supraclavicular nodes are distant, not regional.

1. *Bulky, fused axillary nodes.* Not an absolute contraindication to radical surgical treatment, especially if low in axilla or retropectoral. Fused nodes mean metastases no longer contained within intact lymph nodes, are practically synonymous with distant metastases and should have at least trial with x-radiation.

2. *Extensive apical axillary nodal enlargement.* Sizable nodes at axillary apex are nearly certain indications of more distant spread.

##### (C) DISTANT METASTASES

1. *Supraclavicular lymphadenopathy.* Metastases to nodes above the clavicle are as certain a sign of incurability as is mediastinal node involvement. Enlarged supraclavicular nodes which are suspect, in otherwise operable cases, should be excised for histologic verification before radical operation on the breast.

2. *Pulmonary and Mediastinal.* Routine preoperative chest films should be obtained in all cases in which breast tumors which may be malignant are present.

3. *Skeletal. Order of Frequency:* (1) Ribs; (2) Spine (a) Lumbar, (b) Dorsal, (c) Cervical; (3) Pelvis; (4) Upper Femora; (5) Skull; (6) Humeri. Early metastases to bone are frequently not radiographically apparent. Preoperative skeletal surveys by x-ray are not mandatory except in the presence of persistent pain in possible metastatic sites.

4. *Hepatic.* May be apparent by examination. More frequent in inner quadrant lesions.

5. *Cerebral.* Headache or visual disturbance of progressive sort are usually present.

6. *Other sites.* Uncommon, usually not demonstrable.

##### (D) BIOLOGIC INCURABILITY

Certain forms of mammary carcinoma, approximately 8 to 10 per cent of all cases, are from the beginning rapidly growing and metastasizing and almost invariably lethal in two years or less. Two such lesions distinguished by certain clinical features, and which usually are not benefited by radical operation, may be recognized.

1. *Lesions developing during pregnancy or lactation.* The majority of these neoplasms are rapidly growing, with early regional and frequently distant metastases. Should be treated primarily by x-radiation.

2. *"Inflammatory" carcinoma.* So-called because of resemblance to acute inflammation of breast, with erythema of overlying skin. Such lesions may involve most of the breast in a few weeks. Primary lesion and local metastases are well controlled by x-radiation. Most of such patients die from distant metastases. Radical mastectomy seems to disseminate the disease more rapidly in some instances.

3. *Other anaplastic lesions.* Rapid growth of the primary lesion, or large axillary metastases even with a small breast lesion, may indicate a highly malignant, incurable neoplasm.

Other considerations related to the patient as a biologic unit may constitute inoperability. Severe cardiovascular disease is probably the most common. As in other concurrent disease, the risk must be measured in terms of expected longevity in relation to the anticipated progress of the breast cancer. Age in itself is not a contraindication to radical mastectomy, for many women in their eighth decade developing cancer of the breast have survived that long by reason of a constitutional integrity that enables them to withstand the operation.

#### ADAPTATION OF PALLIATIVE TREATMENT IN TERMS OF GROWTH PATTERN

From the foregoing outline it is apparent that mammary carcinoma is so variegated in its pattern of local growth and metastases that the palliative program must vary to a similar degree. In one patient the problem may be the reduction of growth of the tumor or the healing of ulceration in the breast, so that the impending terminal phase of the disease from distant metastases may be made less distressing. In another the problem may be that of an advanced local lesion of long duration, dilatory growth characteristics and without evidence of distant metastases, in which eradication or control of the local lesion may prolong life by years rather than months. In still others, the problem is that of palliative treatment of metastatic lesions, particularly in bone where adequate control of the disease may result in several more years of useful activity.

The measures available for the effective palliative treatment of breast cancer are still headed by x-radiation, both for the primary and secondary sites. Interstitial radium may be of value in occasional cases. Local surgical measures are of great value in selected patients, and combination of them with irradiation is often indicated. The use of sex hormones is still in an investigative phase, but present knowledge suggests that their status will be as complementary agents to irradiation. There are some distinct hazards in the large doses of androgenic and estrogenic hormone required for effective treatment, but the value of these agents in carefully selected patients, at certain age periods, seems amply demonstrated. The effectiveness of hormonal treatment is, however, highly variable, and the considerable number of therapeutic failures encountered should do much to discourage the premature popularity these agents now enjoy. Otherwise, palliative management requires in the later stages of the disease specific measures for a variety of complications, and an intelligent use of analgesic drugs on a progressive scale of effectiveness and dosage.

As encountered by the clinician, patients for palliative management may be bracketed as follows:

#### 1. Primary Cases

See groups A, B, C, D above

#### 2. Secondary (Post-Operative) Cases

##### Local Recurrence

A. Chest Wall—10-25 per cent of post-operative cases

B. Axillary—5-8 per cent of post-operative cases

C. Distant Metastases—See Group C above

#### CLINICAL MANAGEMENT

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#### 1. A, B, D. Primary Local and Regional Disease

The control of inoperable primary carcinoma of the breast with or without axillary metastases is basically a problem of management with x-ray therapy. X-ray ports are outlined over the primary lesion in such a way that the tumor can be crossfire through at least two ports, care being taken to irradiate as little lung tissue as possible. The axillary and supraclavicular metastases can also be crossfire in a similar way. It is often possible to bring the local and regional disease under clinical control for long periods of time. Five-year survivals without apparent disease have occasionally been obtained in this group of cases but are, of course, unusual. If the patient is young, as she often is, particularly in the biologically incurable group, x-ray castration should be part of the course of x-ray therapy. When there is extensive skin ulceration with associated infection and risk of hemorrhage, the patient not only presents a serious nursing problem but also technical difficulties in irradiation. Frequently it is preferable to do a simple mastectomy, thereby removing the foul, ulcerating mass before x-ray treatment is begun. It is usually possible to close the skin flaps but if necessary a split thickness graft may be utilized to close the defect. The care of the patient is thus much simplified and the palliative end result will be improved.

#### 2. A. Post-operative Skin and Chest Wall Recurrence

It is generally agreed that if extensive post-operative skin or chest wall recurrence develops after a properly performed operation, the disease was not primarily operable, for of course it is not always possible to tell from a clinical standpoint whether a lesion is actually operable or not. If there are but one or two skin metastases, local excision of these lesions with a reasonable margin of normal tissue is probably justified. The treatment of choice, however, is x-radiation. One or two individual metastases in the skin can be treated by small ports using low voltage x-ray. However, since metastases are usually multiple, as a rule it is preferable to treat the entire operative area in which further skin nodules might be expected to develop. Radium needles can be inserted into areas in which there is recurrence in the skin, but there is always the danger of permanent injury to underlying bone and cartilage which sometimes

gives the patient more difficulty than the skin lesions themselves. Recently, some patients with recurrences in skin and soft tissue have been treated with high doses of estrogenic materials, and in some instances this has been followed by complete regression of the clinically apparent disease. Estrogenic therapy probably should be reserved for skin or soft tissue recurrence in elderly women many years post-menopausal who have already received x-radiation and whose skin cannot tolerate further therapy.

### C. 3. *Skeletal Metastases*

The pain incident to skeletal metastases from breast carcinoma is somewhat variable, depending upon the extent and location of the lesions. There may be very extensive bone destruction without any symptoms at all. Occasionally, the first suggestion of bone metastases is a pathological fracture. More often the patient will complain of a dull ache of variable intensity, often worse at night and usually responding at first to mild analgesics. The symptoms of metastases to the spine are often mistaken for those of arthritis until x-ray films show the true nature of the process. Progressive collapse of the vertebral bodies causes pressure on the adjacent nerves, and symptoms of radiculitis then are added to the duller pain of the local disease. At times the patient may complain of severe pain in one of the bones and there may be nothing evident on radiographic examination. It is usually safe to assume in such cases that there is a metastasis present even in the absence of x-ray findings. Early bone metastases are not detectable by x-ray examination. By the time metastatic areas in the bone are discernible by x-ray examination, advanced destruction is present.

Despite the recent wave of enthusiasm for treatment of bone metastases by androgenic therapy, x-radiation still remains the treatment of choice for such lesions. Not only is the relief from pain prompt and lasting but also it is usually possible to arrest the progress of the metastatic lesion, often with complete recalcification. If the patients are pre-menopausal castration is usually indicated. Since x-ray castration seems to be as effective as surgical castration and is far more simply accomplished, it has largely replaced the surgical procedure. Androgenic therapy for skeletal metastases is currently popular. It may be used in any case regardless of the age of the patient. Dramatic response, often apparent within two or three weeks, is usually characterized by relief of pain, increased appetite, gain in weight and a sense of well-being. Unfortunately, the clinical progress of the patient may not parallel the symptomatic improvement and sometimes the metastatic lesions progress rapidly despite the symptomatic palliation. Calcium and Vitamin D have been administered in large quantities in an effort to facilitate the calcification of bony metastases but the end result of this additional therapy has not been convincing and the administration of these agents probably is not justified. In those cases in which there are metastases in the vertebral bodies, a properly fitted back brace will not only give the patient a great deal of relief from

pain but will also protect the injured vertebral bodies from further strain thereby retarding progressive collapse of the bodies and permitting recalcification to take place following x-ray therapy or x-ray and androgenic therapy.

### C. 2. *Pulmonary, Mediastinal and Pleural Metastases*

Occasionally, solitary and well localized metastatic deposits in the lungs may be treated by deep x-ray therapy. The results are unpredictable but at times the metastatic lesion may shrink to a fraction of its former size or entirely disappear. As a rule, pulmonary metastases are multiple and when the pleura becomes involved there is usually associated pleural effusion. If the amount of fluid is small, drainage is not necessary but if the vital capacity of the patient is interfered with by the volume of effusion, thoracentesis will afford a great deal of comfort. This procedure can be done either in the home or the office without the use of expensive or complicated apparatus.

There are isolated reports of regression of pulmonary metastases following both androgen and estrogen therapy, but use of these agents for the control of pulmonary metastases alone does not seem justified.

### C. 4. *Liver and Other Abdominal Metastases*

The treatment of metastatic abdominal deposits from breast carcinoma is discouraging. When ascites develops the patient is not only subjected to abdominal discomfort but there is also elevation of the diaphragm with consequent impairment of vital capacity which may have been diminished already by pulmonary disease. Removal of the ascitic fluid as it collects will not only prevent abdominal discomfort but will relieve dyspnea in a patient with an already diminished vital capacity. Hormone therapy has not been used for the treatment of ascites. Recently we have seen a patient with extensive soft tissue recurrence associated with ascites. She was given high doses of estrogenic substance in the hope that this would control the skin recurrence. There was prompt regression of the skin metastases, and concomitantly the ascites was apparently completely absorbed, suggesting that there was regression of the intra-abdominal metastases also.

### C. 5. *Cerebral Metastases*

Symptoms and signs incident to cerebral metastases depend entirely upon the location of the metastatic lesion. Careful neurologic examination may localize the metastatic deposit quite accurately. In cases where the progress of the disease appears slow and it is possible accurately to determine the site of the metastatic process, it is sometimes feasible to give deep x-ray therapy through small ports to the involved area. Results are extremely variable, but sometimes worthwhile palliation may be obtained.

#### SPECIAL CONSIDERATION OF MANAGEMENT *Hormone Therapy*

The exact role of hormone therapy in the palliative treatment of mammary carcinoma is as yet unknown. It is at present on an experimental basis and care should be taken to be sure that the patient is benefited

rather than injured by such treatment. In light of the facts now known, it appears that patients with metastatic lesions in bone, without regard to age, are entitled to a trial of androgenic therapy. (Such treatment, however, has not replaced the known beneficial results that can be obtained by x-ray therapy to such lesions.) The dosage is usually 100 mg. of testosterone propionate given three times a week until a total of 3600 mg. has been administered, after which the patient is placed on a so called maintenance dose of 100 mg. weekly for an indefinite period. Symptomatic relief, usually apparent within two or three weeks, is characterized by relief of pain, gain in weight, increased appetite, diminished requirement for narcotics and a general sense of well-being. Objective signs of improvement do not necessarily parallel the relief of pain. Androgenic therapy must be controlled by roentgenographic and blood chemistry studies. In favorable cases there may be x-ray evidence of remineralization of the bone, but sometimes this does not occur even though there are subjective signs of benefit. Occasionally, the administration of high doses of androgen will increase the rate of bone destruction, and of course the medication should be stopped promptly in these cases. In the presence of a high value for serum calcium, treatment should be given cautiously. If the serum calcium drops to normal levels a good result can be expected; however, if it remains at a high level or a previously low serum calcium becomes elevated, androgenic therapy should be terminated at once.

Certain masculinizing effects are usually evident with such high dosage of testosterone. These include hirsutism, coarsening of the skin, voice change and often an increase in libido. These changes are most marked in younger women and may be so undesirable to the patient or to the family that continuance of testosterone therapy is not permitted. Occasionally, a patient, especially with high value for blood calcium, becomes intolerant to the drug, developing severe nausea, vomiting and other signs of intolerance, and of course androgenic therapy is not suitable for such patient.

Indications for the palliative use of estrogenic therapy are not yet definite. The information at present available suggests that estrogenic therapy should be reserved for patients in the older age group with soft tissue involvement. Beneficial effects have been largely restricted to regression in the size of inoperable primary lesions and in regression of soft tissue metastases. There appears to be also an improvement in the general physical condition of the patient. This favorable response, when it occurs, appears to be temporary and highly unpredictable. The preparation most commonly used is diethylstilbestrol given orally in doses of 15 mg. daily. Many patients do not tolerate the drug well. Estrogenic therapy should never be used for patients below the age of 60; in pre-menopausal women the administration of it may even accelerate the progress of mammary carcinoma. Frequently large doses of estrogens produce uterine bleeding, necessitating a diminution in the amount of the drug used.

#### *Analgesics and Narcotics*

Properly administered x-ray therapy is probably the most effective method of pain control in advanced cases of mammary carcinoma. When x-ray therapy is no longer effective and it is necessary to supplement its effects by medication, care should be taken in choosing a suitable drug. Many patients, particularly in the older age group, can be expected to live for months or years, and it is wise to reserve the stronger narcotics until they are absolutely necessary. As a rule, aspirin compounds supplemented with codeine are sufficient. Sometimes even aspirin alone will control the early pain. It is often possible to carry the patient on increasing doses of aspirin compounds with codeine up to the terminal stages of the disease. The large amount of codeine required not only diminishes the appetite but also constipates the patient, making special attention to bowel evacuation necessary. When codeine is no longer effective, a change can be made to either demerol, metapon or dilaudid, the choice depending upon the personal preference of the physician and the individual response of the patient to the drug. Some patients have less intolerance for one of the drugs than for another. Methadon, a new synthetic preparation, in doses varying from 2.5 to 10 mg. has been highly effective in the control of pain in the more advanced cases. The drug is less inclined to cause addiction than some of the others and does not interfere with the appetite, is less constipating and is quite inexpensive. Morphine with its euphoric and hypnotic effects should be reserved for the terminal stages of the disease.

#### *Specific Measures for Pain Control*

When there is severe pain originating in areas served by the lumbar and sacral levels of the spinal cord, intrathecal injections of alcohol will often give marked relief over a period of weeks or months. This procedure is of greatest value in cases where the pain is unilateral in distribution, although it may still be utilized when the pain is bilateral. The procedure is quite simple, but not without occasional undesirable sequelae such as disturbances in bladder and anal sphincter control, muscle paralysis and other undesirable complications. Severe localized pain such as that found in association with pathological fractures of the ribs can be effectively controlled by nerve block using one of the synthetic agents dissolved in oil for prolonged relief. Sometimes alcohol injections of individual nerves can be utilized to advantage. Cordotomy, an operative measure in which the spino-thalamic tract is severed, should be reserved for patients whose pain is severe and whose life expectancy exceeds at least six months. The operation, which is technically difficult and carries a certain amount of risk, should be done only on those patients in whom the measure of palliation would justify the procedure. Prefrontal lobotomy is a relatively new operation which has been recommended for intractable pain in certain selected cases. Application of the procedure has been quite limited, and it should be reserved for unusual cases.

## MEDICAL PROGRESS:

### Isotopes in Clinical and Experimental Medicine

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*This is Part II of an article in two parts. Part I appeared in the July issue of California Medicine, and with it were the list of references for the entire article and the Table I referred to in the following text.*

#### IMPORTANT APPLICATIONS OF ISOTOPES IN EXPERIMENTAL MEDICINE

##### General Considerations:

In experimental medicine much the largest part of the work with isotopes has involved their use as tracers. The volume of work in which isotopes have been applied to studies on the biological effects of radiation has been by comparison rather slight. In this section we are limiting ourselves, except in passing comment, to a brief survey of some of the more important tracer studies.

So far investigations have been carried out with stable or radioactive isotopes of 56 of the 96 known elements. The metabolism of most elements known or thought to be essential to living systems has been investigated in varying degree with one or more isotope. In the case of elements known or thought to be necessary in mammalian nutrition ( ${}_1\text{H}$ ,  ${}_6\text{C}$ ,  ${}_7\text{N}$ ,  ${}_8\text{O}$ ,  ${}_11\text{Na}$ ,  ${}_12\text{Mg}$ ,  ${}_15\text{P}$ ,  ${}_16\text{S}$ ,  ${}_17\text{Cl}$ ,  ${}_19\text{K}$ ,  ${}_20\text{Ca}$ ,  ${}_25\text{Mn}$ ,  ${}_26\text{Fe}$ ,  ${}_29\text{Cu}$ ,  ${}_53\text{I}$ , probably  ${}_27\text{Co}$  and  ${}_30\text{Zn}$ , and possibly  ${}_35\text{Br}$ ) some tracer studies have been made on mammals with isotopes of all except  ${}_12\text{Mg}$ ; in fact, only one biological problem, i.e., photosynthesis in higher plants (Ruben, Frenkel, and Kamen<sup>117</sup>), has so far been attacked using a  ${}_12\text{Mg}$  isotope—the radioactive species,  ${}_12\text{Mg}^{27}$ . Work with the stable isotopes,  ${}_1\text{H}^2$  (D),  ${}_6\text{C}^{13}$ , and  ${}_7\text{N}^{15}$  has been very extensive, while but little use has thus far been made of the stable isotopes  ${}_8\text{O}^{18}$  and  ${}_16\text{S}^{34}$ . Fairly or very extensive studies have been carried out with the radioactive species  ${}_11\text{Na}^{24}$ ,  ${}_15\text{P}^{32}$ ,  ${}_16\text{S}^{35}$ ,  ${}_17\text{Cl}^{38}$ ,  ${}_19\text{K}^{42}$ ,  ${}_20\text{Ca}^{45}$ ,  ${}_28\text{Fe}^{55}$ ,  ${}_35\text{Br}^{82}$ ,  ${}_53\text{I}^{130}$ , and  ${}_53\text{I}^{131}$  among elements known or thought to be essential for mammals and with  ${}_38\text{Sr}^{89}$ , which, though not representing an essential element, so far as known, has been used as a substitute for a  ${}_20\text{Ca}$  isotope by reason of the poor yields and difficulties in the measurement of  ${}_20\text{Ca}^{45}$ . Some tracer work has also been done with such unstable species as  ${}_1\text{H}^3$  (T),  ${}_6\text{C}^{14}$ ,  ${}_7\text{N}^{13}$ ,  ${}_11\text{Na}^{22}$ ,  ${}_25\text{Mn}^{52}$ ,  ${}_25\text{Mn}^{54}$ ,  ${}_25\text{Mn}^{56}$ ,  ${}_27\text{Co}^{56}$ ,  ${}_27\text{Co}^{58}$ ,  ${}_29\text{Cu}^{64}$ ,  ${}_30\text{Zn}^{65}$ , and  ${}_53\text{I}^{128}$ , among the essential elements. Of these, T and  ${}_6\text{C}^{14}$  are unquestionably finding extensive use in current research, not yet published upon. In addition a few tracer studies have been carried out on mammals using radioactive species of a number of other elements

(some 33) not known or believed to be essential to man; these are listed in Table I. Studies have also been carried out with isotopes of the non-essential elements  ${}_3\text{Li}$ ,  ${}_5\text{B}$ , and  ${}_80\text{Hg}$ ; but in the case of the first two these have been non-tracer experiments with stable species ( ${}_3\text{Li}^6$  and  ${}_5\text{B}^{10}$ ), and the radioactive isotope  ${}_80\text{Hg}^{197}$  has so far been applied only to the determination of the amount of Hg vapor contaminating the atmosphere of an industrial establishment where mercury was used (Goodman, Irvine, and Horan<sup>40</sup>). In addition there have been extensive toxicological studies with  ${}_88\text{Ra}$  and  ${}_92\text{U}$ .

From the foregoing paragraph it may be seen that a great deal remains to be done with tracers in essentially preliminary work on mammalian metabolism. Aside from the 45 elements for which such isotopic studies are lacking, a number of essential elements have been little more than touched— ${}_25\text{Mn}$ ,  ${}_27\text{Co}$ ,  ${}_29\text{Cu}$ , and  ${}_30\text{Zn}$ . These are "trace elements," and it seems likely that significant advances in our understanding of their metabolic role will come only with development of methods for their study with isotopic tracers. Other elements also deserve intensive investigation; for example, nickel ( ${}_28\text{Ni}$ ), a possibly essential nitrilite, has not been studied isotopically at all, although this deficiency is sure to be soon corrected.

In general, radioactive isotopes offer simpler techniques of application to biological problems than do stable isotopes. This is because the Geiger-Müller counter, with which most of the former may be detected quantitatively, is simpler of operation than the mass spectrometer, with which the latter (except for D and  ${}_8\text{O}^{18}$ ) must be measured. Unfortunately, important elements such as  ${}_7\text{N}$ ,  ${}_8\text{O}$ , and  ${}_12\text{Mg}$  have no unstable isotope of sufficiently long half-life to permit their use in any but very short tracer experiments. However, useful stable species exist for  ${}_7\text{N}$  and  ${}_8\text{O}$  at least, and probably the two rarer species of  ${}_12\text{Mg}$  will also prove very valuable.

In the following subsections the more important studies with isotopes are grouped according to broad categories of elements based upon the significance of the latter in metabolism.

#### Studies on Elements Constituting the Major Organic Metabolites:

**Introduction.** The elements that constitute the major organic metabolites include principally  ${}_1\text{H}$ ,  ${}_6\text{C}$ ,  ${}_7\text{N}$ ,  ${}_8\text{O}$ ,  ${}_15\text{P}$ , and  ${}_16\text{S}$ . Other elements, of course, play important roles in intermediary (i.e., organic) metabolism, but for the purposes of this discussion we are limiting ourselves to the foregoing six.

The use of isotopes as labels of intermediary metabolism was originated by Schoenheimer over a decade ago. He established clearly an important concept—the dynamic state of organic body constituents; in other words, that carbohydrates, fats, proteins, etc., are undergoing a continuous process of breakdown and resynthesis in the living cell, even seemingly inert substances such as stored body fats (see Schoenheimer<sup>122</sup>).

**Carbon.** Three isotopes of  $^{14}\text{C}$  have been used in biological work— $^{14}\text{C}^{11}$  (20.5 minute half-life),  $^{14}\text{C}^{13}$  (stable), and  $^{14}\text{C}^{14}$  (>5,000 year half-life). The first is adaptable only to short-term experiments, whereas the latter two can be used for prolonged studies.

$^{14}\text{C}^{11}$  has found important application in the study of  $\text{CO}_2$  utilization by animals and plants (Buchanan and Hastings<sup>12</sup>; Werkman and Wood<sup>149</sup>; Wood<sup>151</sup>; Ruben and Kamen<sup>119, 120</sup>) and on carbon monoxide metabolism (Tobias *et al.*<sup>141</sup>). The latter authors have shown that  $\text{C}^{11}\text{O}$  is not converted to  $\text{C}^{11}\text{O}_2$  *in vivo* in the human during a period of two hours. An advantage that  $\text{C}^{11}$  has over  $\text{C}^{14}$  is the fact that the penetrating annihilation gamma rays of the former permit convenient *in vivo* measurements whereas the weak beta rays of the latter permit *in vitro* counting only, which for reasonable accuracy must have a rigidly controlled geometry.

$^{14}\text{C}^{13}$  has been used in a rather large series of experiments dealing with the intermediary metabolism of carbohydrates, fats, and, to a lesser degree, amino-acids (Buchanan and Hastings<sup>12</sup>; Vennesland<sup>145</sup>).

$^{14}\text{C}^{14}$  has only recently become available in appreciable quantities—from the nuclear pile reactor—and has not yet had widespread application insofar as published reports are concerned, although the literature is growing rapidly. It promises to be one of the most important of tracer isotopes in studying intermediary metabolism. As examples of the type of syntheses that will become increasingly common may be mentioned the recent work of Reid<sup>113</sup> in synthesizing labeled tyrosine, of Heidelberger *et al.*<sup>55</sup> in synthesizing labeled dibenzanthracene (an important aromatic carcinogen), and Melville, Rachele, and Keller<sup>97</sup> in synthesizing methionine with  $\text{C}^{14}$  in the methyl radical. Recently Bloom, Curtis, and McLean<sup>8</sup> have shown that  $^{14}\text{C}$  administered as carbonate may be laid down at least for several weeks in bone without showing any change in concentration. However, many organic compounds containing labeled  $^{14}\text{C}$  apparently are metabolized very rapidly and do not remain long in the body.

**Hydrogen.** The two tracer isotopes of  $^1\text{H}$ —deuterium or D (stable) and tritium or T (about 30 year half-life)—have approximately the same role to play in studies on metabolism except that a considerable increase in sensitivity of measurement is possible with compounds labeled with T over that with compounds labeled with D.

D has been used to label a wide variety of organic compounds (Schoenheimer<sup>122</sup>; Kamen<sup>70</sup>). It has also been used by Hevesy and Hofer in the form of “heavy water” in the study of the turnover of body water<sup>61-63</sup> and also in the determination of body

water content by the isotope dilution method. These workers found that while a little deuterium appears in the urine within half an hour after ingestion by mouth, the bulk of the water in the body as determined by labeling with heavy water has a half-life of about 9 days, or, otherwise stated, that a given water molecule spends, on the average, about 13 days in the body. Recently Moore<sup>90</sup> with D and Pace *et al.*<sup>107</sup> with T, have also determined total body water in man. In view of the fact that there is no other reliable method for the determination of body water, these isotopes certainly will find wide usefulness in this connection.

T as an organic labeling agent has so far been used only in studies on photosynthesis (Norris, Ruben, and Allen<sup>106</sup>). However, it, as well as D, doubtless has great potentialities in the further unraveling of the vast complexities of intermediary metabolism.

**Oxygen.** No studies with  $^{18}\text{O}$  isotopes have as yet been carried out in mammalian physiology.  $^{18}\text{O}^{18}$  (stable) may be expected to play an important role.

**Nitrogen.** Of the two isotopes of  $^{14}\text{N}$  and adaptable to tracer work— $^{14}\text{N}^{13}$  (10.13 minutes half-life) and  $^{14}\text{N}^{15}$  (stable)—only the latter has had wide application.  $^{14}\text{N}^{15}$  has been used to study respiratory gas exchange by Jones<sup>66</sup>.  $^{14}\text{N}^{15}$  has been widely used in the study of the intermediary metabolism of amino-acids and proteins (Vennesland<sup>145</sup>).

**Phosphorus.** There are more publications dealing with the one useful tracer species of  $^{32}\text{P}$ — $^{32}\text{P}^{32}$  (14.3 day half-life)—than with any other isotope, stable or radioactive. The reason for this lies in the relative ease with which it can be produced (even by bombarding phosphorus with neutrons from a radium-beryllium mixture) its convenient half-life, and the simplicity with which it can be measured (because of its penetrating beta rays).

The major tracer studies with  $^{32}\text{P}^{32}$  intermediary metabolism have been on the formation and fate of two important classes of organic compounds; the phospholipids (Chaikoff and Zilversmit<sup>13</sup>) and the nucleoproteins (Hevesy<sup>59</sup>). The liver has been shown to be the main site of phospholipid production for systemic use, although the kidney and intestinal mucosa synthesize their own phospholipids independently of the liver. Considerable work has been done on the turnover of ribose- and deoxyribose nucleic acid in various tissues. It has been demonstrated that the distribution of labeled phosphate (introduced in the inorganic form) in the nucleic acid moiety of nucleoproteins correlates with the known metabolic activity of the various tissues.

$^{32}\text{P}^{32}$  has also been used in the study of the mineral metabolism of phosphorus (Chievitz and Hevesy<sup>15, 16</sup>; Hevesy, Hahn, and Rebbe<sup>60</sup>). A slow but definite turnover of bone phosphates has been clearly shown. Phosphate excretion is now known to take place through both urine and feces, although less than 10 per cent escapes by the latter route.

Techniques for labeling erythrocytes with  $^{32}\text{P}^{32}$  are known and have been used by Næslund and

Nylin<sup>103</sup> to show that the human placenta in rare cases is permeable to these cells. Labeled cells introduced into the maternal circulation before parturition were later detected in the fetal cord blood. This study may have great significance in relation to the Rh problem.

**Sulfur.** The two isotopes of  $^{16}\text{S}$  that have been used in tracer experiments are  $^{16}\text{S}^{34}$  (stable) and  $^{16}\text{S}^{35}$  (87.1 day half-life).

Heavy sulfur— $^{16}\text{S}^{34}$ , the most abundant of the three rarer isotopes of  $^{16}\text{S}$ —has thus far been produced in small amounts only and consequently has had very limited use. Du Vigneaud *et al.*<sup>28</sup> have synthesized labeled methionine using  $^{16}\text{S}$  slightly enriched with  $^{16}\text{S}^{34}$ , as well as  $^{13}\text{C}^{13}$  (heavy carbon) in the beta-position; these workers were able to show with this doubly labeled material that the  $^{13}\text{C}$  chain of methionine is not utilized in the *in vivo* conversion of methionine to cystine.

Radiosulfur— $^{16}\text{S}^{35}$ , the only unstable species of  $^{16}\text{S}$  of convenient half-life for biological use—has also had limited application, although somewhat more extensive than  $^{16}\text{S}^{34}$ . Its use has been reviewed by Kamen<sup>70</sup>. A number of studies have been carried out in both plant and animal sulfur metabolism. Particularly important has been the work of Tarver and his associates (Tarver and Reinhardt<sup>134</sup>; Tarver and Schmidt<sup>135-137</sup>; Melchior and Tarver<sup>95, 96</sup>) on the synthesis of  $^{16}\text{S}$ -containing amino acids and the metabolism of these and of elemental sulfur in mammals, including the *in vivo* conversion of methionine to cystine and taurine and the distribution of sulfur fed as methionine in the body protein. Most significant of the results of their work and the work of other biochemists using the sulfur label has been the further verification of the dynamic state of body constituents, for a rapid turnover of protein  $^{16}\text{S}$  has been demonstrated, even in the fasting animal. Neither elemental  $^{16}\text{S}$  nor sulfate can be used to form  $^{16}\text{S}$ -containing amino acids. Soluble sulfides are mostly converted to sulfate and thus share the fate of the latter, although a small amount of sulfide may be incorporated into protein as shown by Smythe and Halliday<sup>129</sup> and by Dziewiatkowski<sup>27</sup>.

#### *Studies on Elements Constituting the Major Mineral Metabolites:*

**Introduction.** For our purposes here we are considering the following five elements as constituting the major mineral metabolites:  $^{11}\text{Na}$ ,  $^{12}\text{Mg}$ ,  $^{16}\text{Cl}$ ,  $^{19}\text{K}$ , and  $^{20}\text{Ca}$ ; of these,  $^{12}\text{Mg}$  has as yet received no study with tracers in mammalian physiology.  $^{1}\text{H}$ ,  $^{8}\text{O}$ , and  $^{15}\text{P}$  are also, of course, of major importance in mineral metabolism, but have already been considered in the preceding subsection.

The study of mineral metabolism with tracers began in 1935 with the work of Chievitz and Hevesy<sup>15</sup> on  $^{15}\text{P}$  uptake and distribution in the rat. Since that time a considerable literature has grown up, particularly in regard to electrolyte dynamics and bone metabolism.

**Electrolytes.** Kamen<sup>70</sup> has reviewed the available radioisotopes that may be used in the study of elec-

trolytes. The principal elements involved are in the form of the cations:  $^{11}\text{Na}^{+}$ ,  $^{12}\text{Mg}^{++}$ ,  $^{19}\text{K}^{+}$ ,  $^{20}\text{Ca}^{++}$ ; and the anions:  $^{17}\text{Cl}^{-}$ ,  $^{8}\text{O}^{-}$  as carbonate and bicarbonate,  $^{15}\text{P}$  as the acid phosphates, and  $^{16}\text{S}$  as sulfate—as well, of course, as  $^{8}\text{O}$ , which forms a part of all complex anions. Of these  $^{8}\text{O}$  and  $^{12}\text{Mg}^{++}$  do not, as already indicated, have useful radioactive species.

Of the main essential cations,  $^{20}\text{Ca}$  and  $^{12}\text{Mg}$  are also important bone minerals and organic metabolites. All of the elements involved in the essential anions, with the exception of  $^{17}\text{Cl}$ , also play a role in the intricate dynamics of intermediary metabolism. In addition phosphate and carbonate are, with  $^{20}\text{Ca}$  and  $^{12}\text{Mg}$ , the principal constituents of bone. Therefore, of the elements occurring as electrolytes, it is  $^{11}\text{Na}$ ,  $^{19}\text{K}$ , and  $^{17}\text{Cl}$  that are of interest in metabolism largely because of their status as electrolytes. Most isotope research on the role of electrolytes has been done with isotopes of these three elements and our discussion here will be largely limited to them.

The use of isotopes provides the only method whereby the absolute values for the time of normal penetration and turnover of electrolytes in tissues and cell spaces can be determined. Much of the work so far has been directed toward elucidating these hitherto unsolvable problems.

Two papers of particular significance for the general study of ionic equilibria have been those of Hahn and Hevesy<sup>45</sup> and of Greenberg *et al.*<sup>43</sup> on the rate of penetration of ions through the capillary wall; the latter workers have in addition studied the permeability of the blood-cerebrospinal barrier to ions. Hahn and Hevesy<sup>45</sup> found with labeled chloride, bromide,  $^{11}\text{Na}$ ,  $^{19}\text{K}$ , and phosphate ions injected into the circulation of rabbits, that potassium was by far the fastest to penetrate the capillary wall; from tissue measurements they also concluded that the capillary endothelium in muscle is much more permeable to  $^{11}\text{Na}$  and phosphate than is the endothelium in the brain. Greenberg *et al.*<sup>43</sup> used labeled  $^{11}\text{Na}$ ,  $^{19}\text{K}$ , phosphate, and iodide, which are normal to the body, and  $^{37}\text{Rb}$ ,  $^{88}\text{Sr}$ , and bromide which they considered foreign. Disappearance of these ions from the plasma was in the order:  $\text{K}^{+} = \text{Rb}^{+} > \text{phosphate} > \text{I}^{-} > \text{Na}^{+} > \text{Br}^{-} > \text{Sr}^{++}$ . In the cerebrospinal fluid the increase in concentration followed the order:  $\text{K}^{+} > \text{Na}^{+} > \text{Br}^{-} > \text{Sr}^{++} > \text{phosphate} > \text{I}^{-}$ .

Moore<sup>99</sup> has presented data on the determination of various fluid and tissue volumes of the human body with radioactive tracers of  $^{11}\text{Na}$ ,  $^{17}\text{Cl}$ , and  $^{19}\text{K}$ , as well as with deuterium oxide.

Study of the uptake, distribution and excretion of  $^{11}\text{Na}$  with the short-lived radioactive isotope,  $^{11}\text{Na}^{24}$  (14.8 hour half-life) was first carried out by Hamilton and Stone<sup>64</sup> and by Hamilton<sup>49</sup>. In man, absorption of  $^{11}\text{Na}$  taken by mouth was observed to begin within a few minutes and to be completed, in most cases, in between three and ten hours. In that period excretion was negligible.

Since this initial work there have been a number of studies on the movement of  $^{11}\text{Na}$  across various body and cell membranes. Vischer *et al.*<sup>146</sup> have studied in detail the interchange between the  $^{11}\text{Na}$

ion of the intestinal lumen and the blood and have concluded that the turnover between intestine and blood is very large, being equal to the total plasma  $^{11}\text{Na}$  in approximately 83 minutes. Flexner and his associates have studied in several species the transfer of  $^{11}\text{Na}$  across the placental barrier, including that of the human placenta (Gellhorn, Flexner, and Hellman<sup>34</sup>). In general, they have found that the transfer of  $^{11}\text{Na}$  per unit weight of placenta increases greatly as gestation proceeds.

$^{11}\text{Na}$  is of particular interest as it is present predominantly as an extracellular cation. Manery and Bale<sup>62</sup>, in rats and rabbits, and Kaltreider *et al.*<sup>63</sup>, in man, have shown that within 9-12 hours complete equilibration of injected  $^{11}\text{Na}$  is achieved, its spread from the plasma being rapid for the first two or three hours, and thereafter much slower. Kaltreider *et al.*<sup>63</sup> have given evidence for the view that the volume of fluid involved in the initial spread—averaging about 25 per cent of the body weight in man—represents the extracellular fluid volume.

Of particular clinical interest has been the study done with  $^{11}\text{Na}^{24}$  by Fox and Keston<sup>33</sup> on the mechanism of shock from burns and trauma in mice. These workers have shown that the  $^{11}\text{Na}$  content of injured skin is greatly increased, exceeding the gain in water (edema), and that under conditions of severe injury approximately one-half of the total amount of extracellular  $^{11}\text{Na}$  is side-tracked and rendered unavailable to normal body interchange. They have concluded that the conventional extracellular fluid space has been modified into a much larger "sodium space" including extracellular edema fluid and intracellular water containing excess  $^{11}\text{Na}$ . Fox and Keston also noted a great influx of  $^{11}\text{Na}$  into burned human tissues as determined by *in vivo* measurements at the bedside.

Some use of long-lived radiosodium— $^{11}\text{Na}^{22}$  (of 3.0 year half-life)—has also been made. Reaser and Burch<sup>112</sup> have used it in the study of the retention of  $^{11}\text{Na}$  in congestive heart failure, and Cuthbertson and Greenberg<sup>19</sup> were able to demonstrate the increase of  $^{11}\text{Na}$  space in the rat body under conditions of dietary chloride deficiency. This isotope should prove highly useful in many long-term studies of  $^{11}\text{Na}$  turnover.

There is but a single useful isotope of radio-potassium— $^{19}\text{K}^{42}$  (of 12.4 hours half-life). It has been used in a number of studies on the uptake, distribution, and excretion of  $^{19}\text{K}$ . In contrast with  $^{11}\text{Na}$ ,  $^{19}\text{K}$  is present predominantly as an intracellular cation. Noonan *et al.*<sup>105</sup> have shown that, in rats injected with a labeled 1 per cent potassium chloride solution,  $^{19}\text{K}$  ion penetrates rapidly into most tissues of the body, the rate being highest for liver, heart, kidney, lung, diaphragm, and gastrointestinal tract, intermediate for the general musculature and skin, and low for testes, erythrocytes, and brain. In tissues with rapid penetration, the total  $^{19}\text{K}^{42}$  has a relative activity higher than the simultaneous plasma value during the first one to two hours; this is particularly marked after intraperitoneal injection. Fenn *et al.*<sup>32</sup>, in a subsequent paper, verified these observations in

the rabbit, cat, and dog. They concluded that an excess of  $^{19}\text{K}$  in the plasma is quickly removed by the viscera, together with an anion, and is slowly released to the muscles.

Studies with radiochloride have been carried out thus far with one of the short-lived isotopes— $^{17}\text{Cl}^{38}$  (of 37 minute half-life). The long-lived species— $^{16}\text{Cl}^{36}$  (about 1,000,000 year half-life)—now available from the pile, may be expected to prove of considerable value. Manery and Haege<sup>63</sup> have studied the penetration of labeled chloride, administered as lithium chloride, into the tissues of the rat and rabbit. They have found that, after intravenous administration, equilibrium is reached within a few minutes in such organs and tissues as the kidney, liver, muscles, cartilage, and tendon, but that  $^{17}\text{Cl}^{38}$  does not enter the entire chloride-containing phase of testes and pyloric mucosa even in one hour.

From the studies cited it can readily be seen that the use of tracers has a vital role to play in the elucidation of problems in electrolyte dynamics.

**Bone metabolism.** The most abundant elements in bone are  $^{6}\text{C}$ ,  $^{8}\text{O}$ ,  $^{12}\text{Mg}$ ,  $^{15}\text{P}$ , and  $^{21}\text{Ca}$ . Of these only  $^{20}\text{Ca}$  need be considered here, and with it  $^{38}\text{Sr}$ , which has been used as auxiliary label for  $^{20}\text{Ca}$  by virtue of the metabolic similarity of these two elements and certain practical advantages of  $^{38}\text{Sr}^{89}$  over  $^{20}\text{Ca}^{45}$ .

The single isotope of  $^{20}\text{Ca}$  so far used is the unstable species  $^{20}\text{Ca}^{45}$  (180 day half-life). It has been applied in several studies on the uptake of  $^{20}\text{Ca}$  by osseous tissues.  $^{20}\text{Ca}^{45}$  is stored almost entirely in bone (Pecher<sup>108</sup>; Greenberg<sup>42</sup>). Vitamin D has been shown to promote the absorption of  $^{20}\text{Ca}$  from the digestive tract and the mineralization of the bones of rachitic rats.

$^{38}\text{Sr}^{85}$  (65 day half-life) has been used in a number of studies on bone metabolism. Upon injection  $^{38}\text{Sr}$  rapidly concentrates in the skeleton, being at 24 hours about 100 times greater there per unit weight than in the soft tissues (Pecher<sup>108</sup>). Studies on bone fracture healing (Copp and Greenberg<sup>18</sup>) have shown that recalcification, as judged by  $^{38}\text{Sr}^{85}$  uptake, is less active in vitamin A and D deficient and D hypervitaminotic rats than in normal rats.

#### *Studies on the Essential Trace Elements:*

**Introduction.** The best known trace elements in mammalian physiology are  $^{26}\text{Fe}$  and  $^{53}\text{I}$ .  $^{25}\text{Mn}$  and  $^{29}\text{Cu}$  are also known to be essential; and evidence for  $^{27}\text{Co}$  and particularly  $^{30}\text{Zn}$  is almost conclusive. Some evidence also exists that  $^{35}\text{Br}$  and possibly  $^{28}\text{Ni}$  may be essential micronutritiles. Although fluorine ( $\text{F}$ ) is known to aid resistance to dental caries, there is no evidence as yet that it plays an essential role. Considerable amounts of silicon ( $^{14}\text{Si}$ ) and aluminum ( $^{13}\text{Al}$ ) occur in the vertebrate body, but no requirements have been demonstrated for these elements.

Of the essential trace elements only  $^{26}\text{Fe}$  and  $^{53}\text{I}$  have been extensively studied with tracers.

**Iron.** Two radioactive species of  $^{26}\text{Fe}$ — $^{26}\text{Fe}^{55}$  ( $\sim$  4 year half-life) and  $^{26}\text{Fe}^{59}$  (47 day half-life) have been used in tracer experiments.  $^{26}\text{Fe}$  metabolism,

particularly as studied with tracers, has recently been reviewed by Hahn.<sup>46</sup>

Of particular medical interest has been work on blood preservation as studied with both  $^{26}\text{Fe}$  isotopes. Gibson *et al.*<sup>35, 36</sup> have done extensive studies on the use of various preservatives in relation to the survival of transfused cells after *in vitro* storage. They have found that refrigeration, the addition of dextrose to the citrate anticoagulant, the maintenance of a slightly acid reaction of the diluted plasma or resuspension fluid, and optimal dilution are essential for prolonged preservation. In certain acid-citrate solutions whole blood can be safely preserved with up to 70 per cent viability for three weeks. Cells preserved by the simple addition of citrate are almost entirely broken down within 24 hours in the new host after only two weeks of preservation *in vitro*, as first shown with radioiron by Ross and Chapin<sup>110</sup>. Other significant studies have been the determination of red cell and plasma distribution and volume with radio-iron-labeled erythrocytes by Gibson *et al.*<sup>37-39</sup> and the demonstration by Moore *et al.*<sup>98</sup> and Hahn *et al.*<sup>47</sup> that ferrous  $^{26}\text{Fe}$  is better absorbed from the gastrointestinal tract than ferric  $^{26}\text{Fe}$ .

*Iodine.* Three  $^{131}\text{I}$  species, all radioactive, have been used in tracer studies— $^{131}\text{I}^{128}$  (24.99 minute half-life),  $^{131}\text{I}^{130}$  (12.6 hour half-life), and  $^{131}\text{I}^{131}$  (8 day half-life). Most work at present is being done with the last of these.  $^{131}\text{I}$  metabolism in the mammal, particularly as studied with tracers, has recently been reviewed by Leblond<sup>34</sup>.

The  $^{131}\text{I}$  label has permitted the solution of many vital problems relating to the physiology of the thyroid gland. Before radioiodine became available, the entrance of  $^{131}\text{I}$  into the gland could not be studied under physiological conditions. When minute doses are administered to the mammal, a high proportion becomes incorporated into the gland—about 60 per cent in the rat by 24 hours and about 50 per cent in man. Among the many other important problems of thyroid physiology that have been solved may also be mentioned the recent demonstration by Taurog and Chaikoff<sup>138</sup> that the circulating hormone in the plasma is almost certainly thyroxine.

Reiner *et al.*<sup>114</sup> have been able to study the absorption rates of insulin labeled by coupling it with diazotized iodoniline containing radioiodine. A correlation was found between the differences in absorption rate and the intensity of hypoglycemic action produced. In the preparation used, absorption was found to be in the following order: insulin > globin insulin (with zinc) > protamine zinc insulin.

*Other trace elements.* Few studies have been carried out with isotopes of  $^{25}\text{Mn}$ ,  $^{27}\text{Co}$ ,  $^{29}\text{Cu}$ , and  $^{30}\text{Zn}$ . Representative studies are cited in Table 1. Some studies using radioactive  $^{35}\text{Br}$  have already been mentioned under the discussion of electrolytes. Also worthy of special note is the demonstration with  $^{35}\text{Br}^{82}$  (34 hour half-life) that bromine is concentrated in the thyroid (Perlman, Morton, and Chaikoff<sup>100</sup>).

#### *Studies on Elements Not Known to be Essential in Mammalian Nutrition:*

At least 78 elements are not known or believed to be directly essential for mammals, although the need of various plants for other elements, especially boron ( $^{10}\text{B}$ ) and molybdenum ( $^{42}\text{Mo}$ ), has been conclusively demonstrated, also the need of certain lower animals for such elements as vanadium ( $^{24}\text{V}$ ), silicon ( $^{14}\text{Si}$ ), etc. A minority of these 78 elements has been studied in mammals with isotopic tracers—in connection with their behavior when present either in trace or toxicological amounts. It is interesting to speculate as to how many elements will eventually be found to be essential in trace amounts.

For over 45 years there has been interest in the biological effects of the naturally occurring radioactive elements, particularly  $^{88}\text{Ra}$ ,  $^{90}\text{Th}$ , and  $^{92}\text{U}$ . In the case of  $^{88}\text{Ra}$  in particular, there have been many studies on its distribution after injection or ingestion in mammals; assays for the contents of these elements in tissues have, in most cases, been made with various techniques of measurement for radioactivity. The literature on  $^{88}\text{Ra}$  and  $^{92}\text{U}$  up to 1933 has been reviewed in detail in the book by Stoklasa and Penkava<sup>131</sup>. However, the main emphasis of these studies has been investigation of the toxic and radiation effects of the heavy radioactive elements rather than tracing their fate in the body. One important fact deriving from these studies has been that  $^{88}\text{Ra}$ , like many of the heavy metals, is deposited in bone and, by its chronic radiation effects, there may induce malignant change (cf. Lisco *et al.*<sup>86</sup>, in the case of  $^{88}\text{Sr}$  and  $^{94}\text{Pu}$ ). These effects are reviewed by Stoklasa and Penkava.

Recently there has been considerable interest in the fate *in vivo* of trace amounts of elements now thought to be nonessential or foreign to the mammalian body. In such experiments the amount of the labeled element introduced should be so small as to have no manifest toxic or pharmacological effect and no detectable radiation effect on the organism as a whole. So far 29 nonessential elements have been studied on this basis: beryllium ( $^{4}\text{Be}$ ), fluorine ( $^{19}\text{F}$ ), argon ( $^{18}\text{A}$ ), arsenic ( $^{75}\text{As}$ ), selenium ( $^{75}\text{Se}$ ), krypton ( $^{86}\text{Kr}$ ), rubidium ( $^{87}\text{Rb}$ ), strontium ( $^{88}\text{Sr}$ ), yttrium ( $^{89}\text{Y}$ ), zirconium ( $^{90}\text{Zr}$ ), columbium ( $^{91}\text{Cb}$ ), molybdenum ( $^{92}\text{Mo}$ ), ruthenium ( $^{94}\text{Ru}$ ), antimony ( $^{115}\text{Sb}$ ), tellurium ( $^{122}\text{Te}$ ), xenon ( $^{134}\text{Xe}$ ), cesium ( $^{133}\text{Cs}$ ), barium ( $^{138}\text{Ba}$ ), lanthanum ( $^{147}\text{La}$ ), cerium ( $^{145}\text{Ce}$ ), praseodymium ( $^{149}\text{Pr}$ ), element 61, gold ( $^{191}\text{A}$ ), lead ( $^{208}\text{Pb}$ ), bismuth ( $^{208}\text{Bi}$ ), astatine ( $^{85}\text{At}$ ), radon ( $^{220}\text{Rn}$ ), thorium ( $^{232}\text{Th}$ ), protoactinium ( $^{231}\text{Pa}$ ), neptunium ( $^{233}\text{Np}$ ), plutonium ( $^{239}\text{Pu}$ ), americium ( $^{243}\text{Am}$ ), and curium ( $^{244}\text{Cm}$ ). Citations for these studies are included in Table 1 under the respective elements.

Certain of the foregoing studies have particular medical significance. Hamilton<sup>50</sup> who has studied the distribution in rats of a large number of the above elements administered in trace amounts, has demonstrated with radioisotopes the selective localization of many in bone—particularly of  $^{89}\text{Y}$  and  $^{145}\text{Ce}$  (fission products) and  $^{94}\text{Pu}^{239}$  (a product of  $^{92}\text{U}^{238}$

neutron capture); these elements are excreted very slowly and have biological half-lives in the body of from one to three years. Since they are long-lived species and are abundantly produced in the pile, they constitute a potential health hazard for the personnel of atomic energy installations.

The use of radioisotopes has been of considerable value in showing the distribution of nonessential elements used in pharmacology. For example, Bertrand and Tobias<sup>7</sup> have demonstrated with radiogold that the uptake of gold sodium thiosulfate in the synovia and synovial fluid of a patient suffering from rheumatoid arthritis, and of rabbits in which chemical (turpentine) arthritis has been induced, was very marked, while, in the case of control animals, uptake was somewhat less. Such studies are of value in relation to the use of  $^{75}\text{Au}$  salts in rheumatoid arthritis. The use of radioantimony— $^{51}\text{Sb}^{124}$ —by Brady *et al.*<sup>11</sup> in the study of *Dirofilaria immitis* infection (filariasis) in dogs, has shown that sodium antimony xylitol is taken up in significant amounts by the adult worms, which concentrate it only less than the thyroid and liver. Similar studies

with radioarsenic— $^{33}\text{As}^{74}$ —by Lawton *et al.*<sup>83</sup> on *Litosomoides carinii* infection (filariasis) of the cotton rat, have shown the concentrating of sodium arsenite by the parasites. Such studies can be expected to aid in our understanding of the mechanism of many pharmacological agents and may possibly point the way toward the development of new techniques.

$^{35}\text{Br}$ , an element that possibly plays an essential role in animal nutrition, has been used in radioactive form to label a number of dyes. For example, Moore and Tobin<sup>100</sup> have been able to show by this means the selective localization of labeled and dibrom trypan blue in inflammatory lesions.

In summary, it may be noted that, in the application of radioactive isotopes of the majority of elements to biological problems, we are still in a primitive stage. Before the wide adoption of these new techniques a new generation of workers must be trained. The field has just opened up, and the future will see much further work and many important discoveries.

*The list of references for this article appeared at the end of Part I which was printed in the July issue of California Medicine.*

**California Cancer Commission Studies\***  
**Chapter XXI**

**Cancer of the Anus, Rectum and Rectosigmoid**

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THIS chapter will be limited, insofar as anatomical boundaries and symptoms permit, to discussion of cancer of the anus, rectum and rectosigmoid. The rectosigmoid has no definite landmarks, but will be considered to comprise that portion of the bowel above the ampulla of the rectum and below the movable portion of the sigmoid, the upper part lying at and just above the pelvic peritoneal reflection.

**INCIDENCE**

According to the Bureau of Vital Statistics, cancer of this area is ranked number four in frequency among all cancers of the body. In 1890 there were two deaths per 100,000 population reported as caused by cancer of the anus, rectum and rectosigmoid, and in 1940 6.7 deaths per 100,000 were reported from this cause. This apparent increase, however, may be accounted for, in part at least, by better clinical and postmortem diagnosis.

The majority of patients with this disease are between 50 and 75 years of age, but 20 per cent are under 50. About 3 per cent of cancers in this area of the body occur in patients between the ages of 20 and 30. It is in this decade of life that they are most often overlooked and for this reason are either inoperable or incurable when the diagnosis is made. There is no "cancer age."

**DIAGNOSIS**

There are few early signs or symptoms. Symptoms commonly related by patients are change in bowel function (especially frequency, which is too often called diarrhea, or dysentery) with an unsatisfied desire to stool; the passage of blood and mucus; abdominal discomfort; loss of appetite; nausea and vomiting. Pain is not marked except in anal lesions.

Often the patient reports rectal bleeding, and this should never be attributed to hemorrhoids without a digital, proctoscopic examination and roentgen studies to rule out the presence of more serious lesions higher in the bowel.

Proper palpation of the rectum with the patient in the lateral position will reveal 80 per cent of the lesions in this area. The lesion may be a polyp, with a pedunculated or sessile base, a broad flat soft villous adenoma, a polypoid mass, a craterlike ulcer with hard margins or an annular lesion involving all surfaces of the bowel. (See Figure 1.) By use of the sigmoidoscope these lesions can be visualized.

Cancer at the anal opening may resemble a chronic anal ulcer with an indurated base, and may originate in the perianal and perirectal glands as an adenocarcinoma, or from the anal integument as an epitheli-

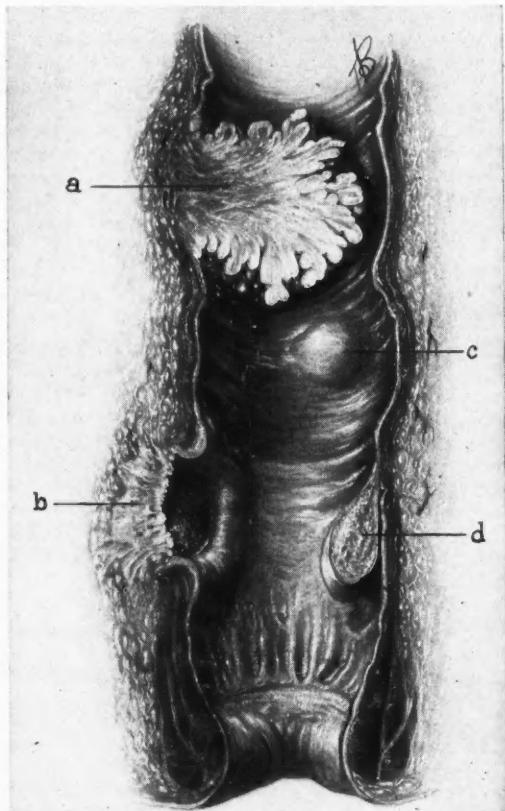


Figure 1. Drawing illustrating: (a) Polypoid carcinoma with moderate involvement of the bowel wall, (b) Ulcerating carcinoma with marked penetration of bowel wall and with rolled up edges, (c) Adenoma which may become a polyp or a cancer, (d) Benign polyp on short pedicle. The mucous membrane is normal.

oma (epidermoid carcinoma). (See Figure 2.) The epithelioma may metastasize to the inguinal nodes, as well as spread upward in the perirectal spaces.

*All suspicious lesions should be biopsied. If the first specimen is negative the biopsy should be repeated.* Sigmoidoscopic examination should be done under intravenous anesthesia if the instrument cannot be passed to eight inches, especially if bleeding is a constant symptom. Negative findings in a roentgen examination with barium enema are not conclusive in the lower eight inches of the colon and may be dangerously misleading because a filling defect is usually obscured by other loops of bowel. A barium enema should never be given preceding the sigmoidoscopic examination. When given at any time it

\*Organized by the Editorial Committee of the California Cancer Commission.

should be done with caution lest a partial obstruction be made total.

Pathologists differ widely in the diagnosis of adenomas and polyps. Many classify them as Grade I

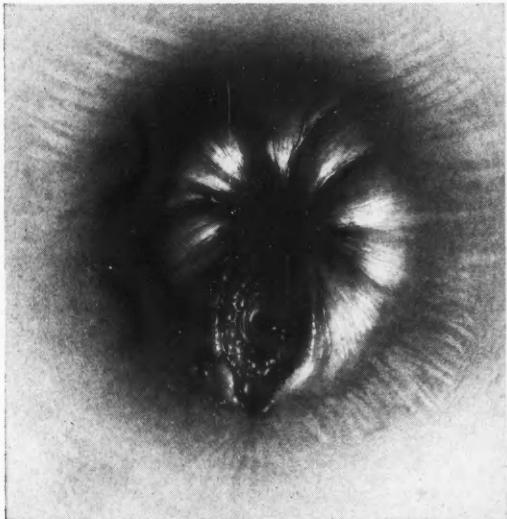


Figure 2. Anal epithelioma, or epidermoid carcinoma. Shows ulceration of anal integument involving deep structures. May resemble other anal ulcerative lesions.

carcinomas, whereas others will call the same lesions benign. (Figure 3.) These lesions should always be regarded at least as premalignant.

The grading of frank adenocarcinomas should not influence the treatment; whatever the grade, radical removal is indicated. (Figure 4.)

Differential diagnosis must be made from sarcomas (rare), metastases from upper abdominal lesions (stomach, pancreas, ovary, uterus, bladder, colon), prostatic disease, from ulcers due to X-ray or radium therapy, from chronic infection such as amebic granulomas, lymphogranuloma inguinale, chronic ulcerative colitis, ordinary chronic anal fissures and tuberculosis and luetic ulcers. Biopsies are necessary to rule out carcinoma.

#### TREATMENT

The patient is entitled to every means for a cure and should not be denied an exploratory procedure unless the case is utterly hopeless. The object of treatment is to cure the cancer or prolong life for a maximum period with a minimum of disability and discomfort. The patient should be informed of the seriousness of his condition and that his cooperation is essential for recovery. The patient who is a poor surgical risk should be built up generally so that he can stand the radical procedure. Occasionally it may be necessary to do the operations in two stages.

Operability and curability must be determined by

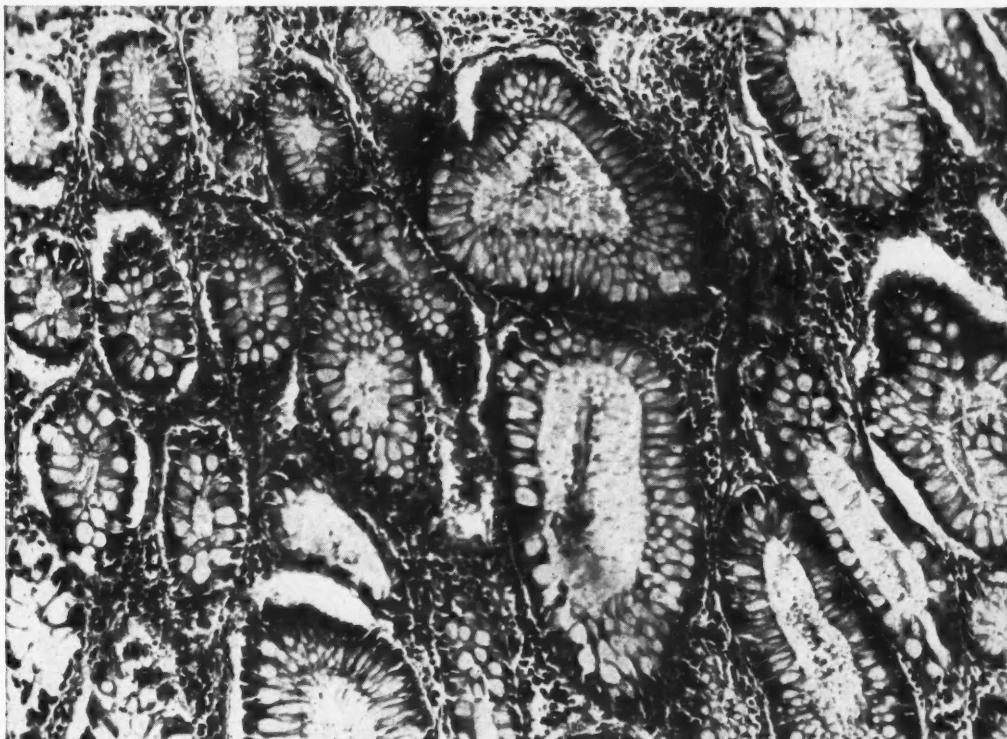


Figure 3. Adenoma of rectum (x 65) normal glandular epithelium at left. To right adenomatous epithelium exhibiting slight hyperchromatism of nuclei and almost perfect polarity but producing larger imperfectly shaped glands.

an evaluation of all the factors concerned, such as age and general condition of patient, type, size and location of growth, and the presence of metastases. Small movable tumors are often more likely to spread earlier than those which have become surrounded by inflammatory tissue. A tumor which may be resectable may be inoperable because of the poor general condition of the patient. Curability can be estimated only in the absence of demonstrable metastases.

Cure of cancer of the rectum involves many factors. Cancer cells infiltrate locally and spread to remote areas by way of lymphatics and veins, therefore the most radical removal of the growth with the structures which transmit these cells is essential, even though it entails complex changes in the anatomy of the individual. The surgeon should be competent to perform all accepted procedures, and should be capable of planning and carrying out the operation best suited to the individual patient.

A number of surgical procedures require a permanent abdominal colostomy. To obviate the necessity of the abdominal artificial anus (which the patient and his medical advisors are still somewhat loath to accept because of the unfounded stigma at-

tached to it or because they have not been trained in its management), many procedures have been tried and many found inadequate or undesirable. An uncontrollable perineal anus has been proven less practical than one in the abdomen, which can be managed with much less effort. The objections to an abdominal anus are unfounded. A properly constructed colostomy, irrigated thoroughly every other day will not be odorous nor will it soil the patient's clothing.

#### ABDOMINOPERINEAL RESECTION

The present consensus is that the combined abdominoperineal resection of the rectum and rectosigmoid with a permanent abdominal colostomy offers the best chance of cure in the majority of cases. The one-stage procedure is the method of choice in good risks. For those in whom medical decompression of an obstructed colon has not been successful, a cecostomy or transverse colostomy should be done and this followed in a short time by the combined abdominoperineal resection. (Figure 5.)

#### COLOSTOMY AND POSTERIOR RESECTION

Another method, the colostomy and posterior resection, is suitable for removal of low growths in

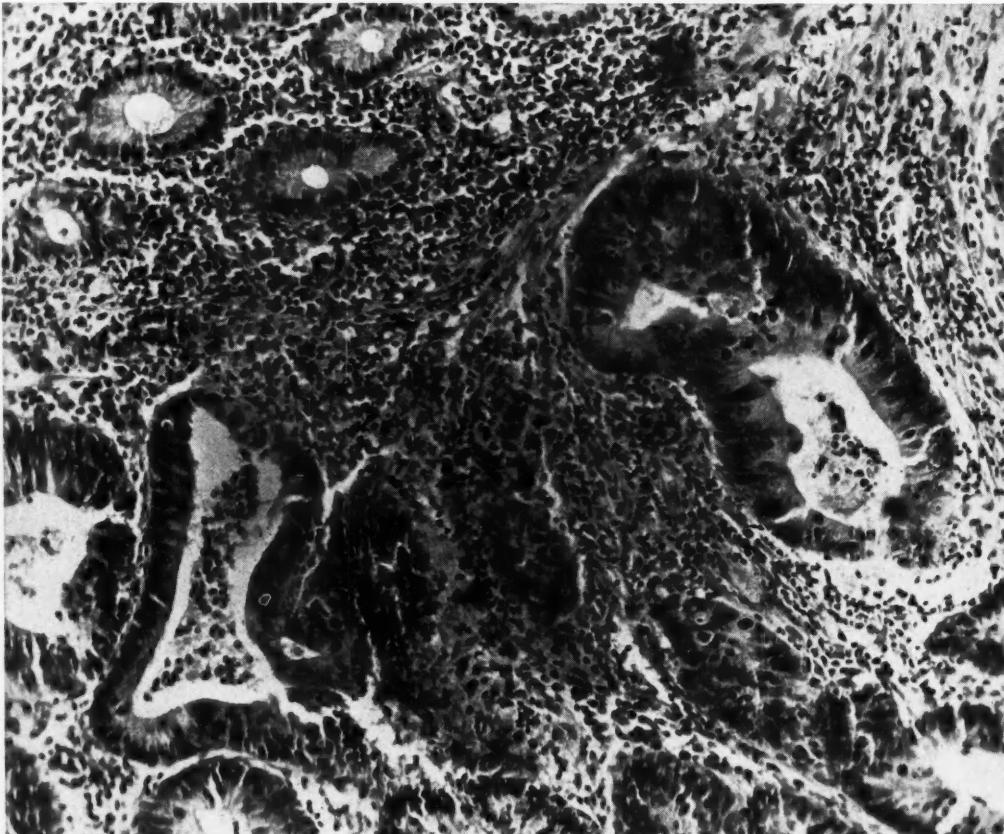


Figure 4. Adenocarcinoma of rectum (x 75) grade II malignancy. Normal glandular tissue at upper left. Tumor tissue at right exhibits very irregular glands made up of cells exhibiting marked hyperchromatism, occasional abnormal mitoses and loss of polarity. The stroma is considerably infiltrated by leukocytes.

certain patients who are *poor surgical risks* because of cardio-circulatory-renal impairment or in patients who are at an age at which the expectancy of life is limited. The amount of the bowel and lymphatic structures removed is not as great as the amount removed in the abdominoperineal procedure.

#### COLOSTOMY AND ANTERIOR RESECTION

High rectal and rectosigmoid growths, in the presence of metastases, may be removed by anterior resection, the lower rectal stump being *left in situ*. A permanent abdominal colostomy is established.

#### ANTERIOR RESECTION WITH END-TO-END ANASTOMOSIS

Several surgeons have advocated and performed resections of lesions in the rectosigmoid and upper rectum with reestablishment of continuity of the bowel, with or without complementary temporary colostomy. This would be the ideal procedure if it did not jeopardize the chance of cure by failing to remove all the cancer-carrying elements. Several techniques for this operation have been described, the merits of which cannot be determined without the test of time. Constriction of the anastomotic site is one of the disadvantages of this procedure.

#### PROCTOSIGMOIDECTOMY WITH PRESERVATION OF ANAL SPHINCTERS

Abdominoperineal resection without abdominal colostomy and with preservation of the anal sphincter (so-called "pull-through operation") is the method of choice with some surgeons in selected cases. The lesion must be far enough above the anus

(2 or 3 inches) to insure removal of downward lymphatic spread, and the length of the viable sigmoid must be adequate to reach well beyond the anal outlet. There is considerable controversy concerning the degree of bowel control following this procedure.

Anal epitheliomas (Figure 6) are treated by radical surgical removal (abdominoperineal resection) followed by block dissection of both inguinal regions.

A curative, and also a preventative, procedure is the destruction of all adenomas, polyps and papillomas by cauterization or desiccation. Removal of all such lesions is essential in the preventative program.

Other methods of treatment—local excision, colostomy and perineal excision, cauterization, fulguration and irradiation—should be considered as palliative and not curative. Colostomy relieves obstruction only. The removal of the primary lesion, even in the incurable, affords a comfort to body and mind that is worth the hazard and effort.

#### MANAGEMENT

Success depends upon a correlation of all clinical tests: complete blood examination; blood chemistry determinations; estimation of nonprotein nitrogen; determination of prothrombin level; serum albumin and liver function tests when liver damage is suspected. The internist or cardiologist should interpret the electrocardiogram tracings and physical findings in terms of surgical risk. It is essential to have an x-ray film of the chest. Finding of a small or moderate metastasis does not contraindicate removal of

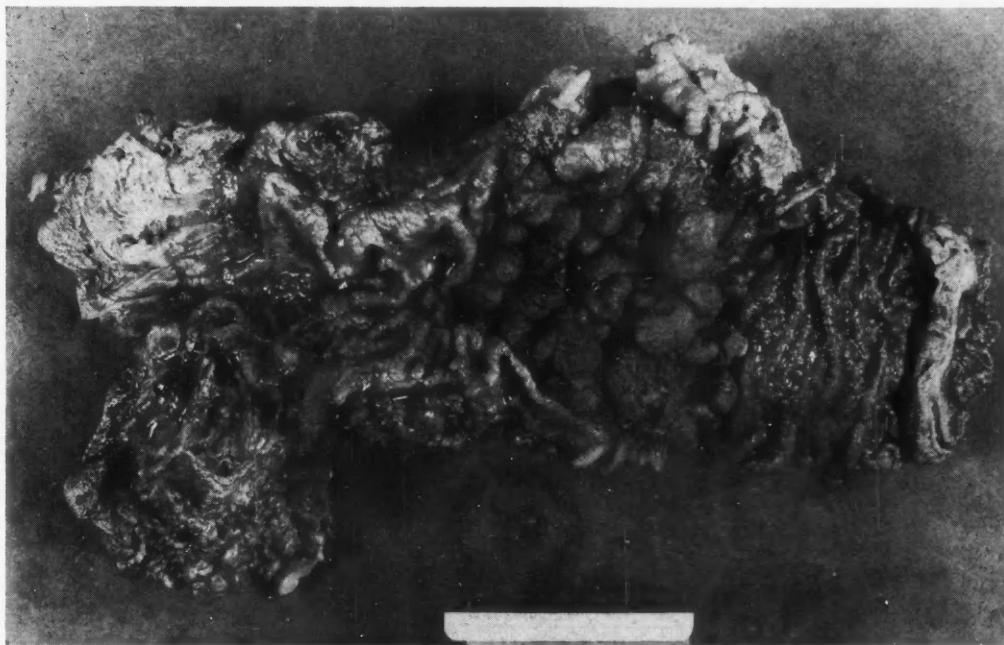


Figure 5. Photograph of excised rectum with annular ulcerating nodular lesion involving the mid-portion.

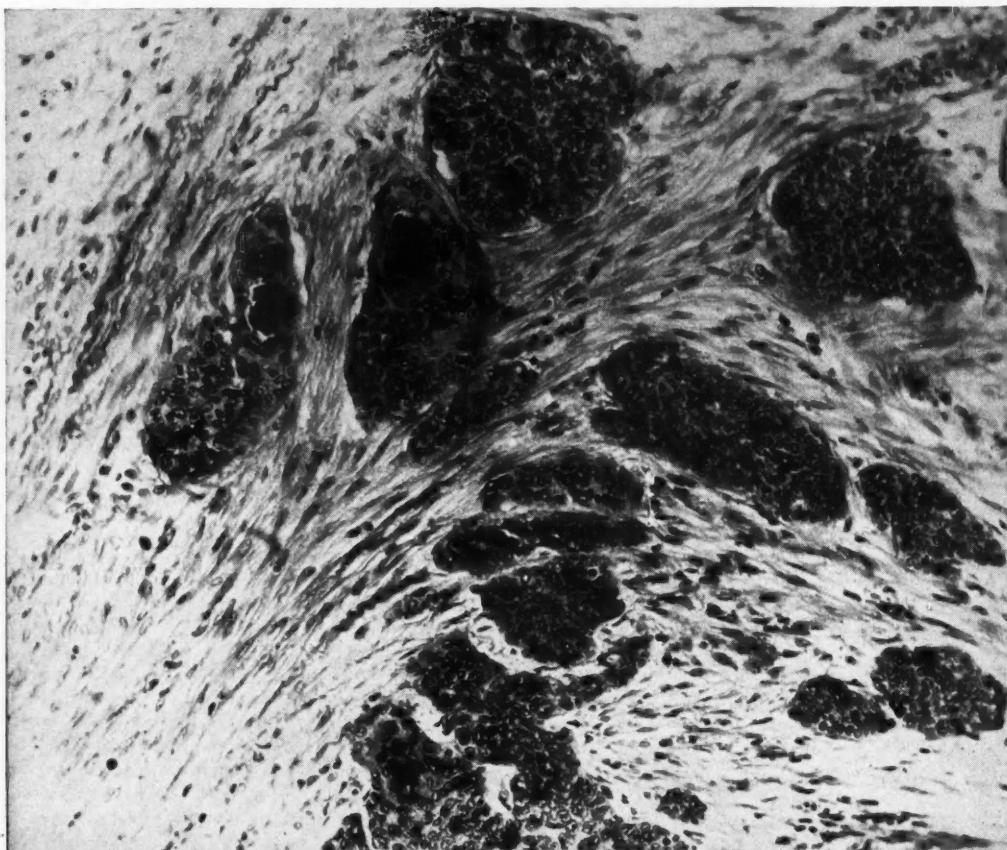


Figure 6. Epidermoid carcinoma of anus (x 70). There is no normal tissue present for comparison. The lesion is composed of irregular masses of squamous cells in the centers of some of which are masses of keratin, "epithelial pearls" (black in photograph).

the primary lesion. Cystoscopic study of the bladder, ureters and kidneys is essential in the presence of growths which may involve these organs. Vitamin deficiencies must be corrected, and anemia, which is a common finding, must be overcome by repeated transfusions of whole blood.

The bowel must be decompressed by saline irrigations, mineral oil and castor oil. A sulfa drug (sulfasuxidine at present is most favored) is given in appropriate doses for approximately one week before operation. This is essential in those cases in which a resection and anastomosis is contemplated. Thorough decompression is of paramount importance in all cases because the handling of a distended bowel predisposes to peritonitis with all its sequelae, especially small bowel obstruction.

Postoperative care entails a careful watch for and prompt treatment of such complications as shock, atelectasis, hemorrhage, circulatory collapse, phlebitis, obstruction, peritonitis and embolism. When whole blood is not available to combat shock, plasma and washed red cells are valuable.

#### SUMMARY

1. There is no "cancer age."
2. Any abnormal manifestation of bowel function should be considered to be the result of onset of cancer until cancer is disproved.
3. Routine thorough rectal palpation and instrumental examination are essential.
4. X-ray examination, especially with barium enema, should never be carried out prior to a sigmoidoscopic examination when cancer of the rectum is suspected.
5. The surgical procedure should be selected for each individual.
6. The growth should be removed whenever possible.
7. Proper preoperative and postoperative management is essential in decreasing morbidity and mortality.

*"Cancer of the Liver, Gallbladder, and Extrahepatic Ducts, and Pancreas"* by William F. Rowe, M.D., and E. Eric Larson, M.D., Chapter XXII of the California Cancer Commission Studies, will appear in this section in the September issue of CALIFORNIA MEDICINE.

# California MEDICINE

OWNED AND PUBLISHED BY THE CALIFORNIA MEDICAL ASSOCIATION  
450 SUTTER, SAN FRANCISCO 8      PHONE DOUGLAS 2-0062

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For Information on Preparation of Manuscript, See Advertising Page 2

## EDITORIALS

### Hospitals in Practice

Of tremendous interest to all physicians, and of specific interest to those who practice as salaried employees of hospitals, is the opinion rendered last May 19 by the office of the Attorney General of the State of California.\* This opinion, given in response to a request by the State Board of Medical Examiners, holds in no uncertain language that a non-profit hospital is not permitted by law to engage in the practice of medicine and that the employment of physicians on a salary basis, with the hospital billing and collecting from the patients, is an illegal act which is specifically prohibited by law.

The case in point arises from an inquiry from a non-profit hospital association which sought this opinion before proceeding to employ a pathologist on a salary basis. The opinion leaves no room for doubt that such employment constitutes the practice of medicine and that such practice is illegal, whether performed directly or indirectly. It also reemphasizes earlier court decisions to the effect that the practice of pathology is a diagnostic procedure which is as much a part of the practice of medicine as the giving of remedies.

The California Medical Association has long held that the practice of medicine by hospitals, particularly through the employment of pathologists, radiologists and anesthesiologists, is a violation of both ethical and legal requirements. Nevertheless, many hospitals have found such practices to be financially profitable and have extended such employment to the furthest possible point. It now appears that such hospitals will have to reevaluate their individual positions and make new arrangements with the pro-

fessional men practising within the hospital properties. The Association has long contended that there is no essential difference between the employment of pathologists on a salary basis by such hospitals and the employment of obstetricians, surgeons or other physicians who confine their activities to one specialty. The opinion of the Attorney General's office bears out this conclusion in every detail and should do much to clear up a growing tendency to exploit physicians.

The medical profession in California has gained immeasurably by this opinion in its effort to keep the practice of medicine a free enterprise, not under the domination or control of outside groups or interests, either private or governmental. The Hon. Fred N. Howser, California's able Attorney General, is to be commended on his sincerity, forthrightness and courage in issuing this opinion in the interests of sound professional practice.

### What Is the C.M.A.?

From time to time some members of the California Medical Association propound the above or similar questions, seeking to learn just what it is that the Association does in return for the dues paid by the members. This has been particularly true in recent years, when the dues have been at a higher level than in prewar years.

From time to time various answers to this question have been formulated and distributed. The answers were not always the same but in general they followed the same pattern and hit the same high spots.

\*This opinion will be found in full on p. 172 of this issue.

Now, in response to an inquiry by the Collector of Internal Revenue, the Association has again digested its activities. Once more some concentrated thought has been put into this subject and an up-to-date answer given to the recurring question.

To those members who may have asked or thought of this question, even though not asking it, the digest

of C.M.A. activities appearing on page 161 of this issue should be of interest. To other members who may not have had this question cross their minds, a review of C.M.A. activities is still a good project. A few minutes spent on this digest, a little thought given to the subject matter covered, would be a good investment in recommended reading.



## Letters to the Editor . . .

The Editor  
CALIFORNIA MEDICINE

Dear Sir:

In the May issue of CALIFORNIA MEDICINE appears an article entitled "A Therapy of Proved Efficacy in Otomycosis" by Ben L. Bryant of Los Angeles. The remarkable thing about this article is the fact that a series of cases is reported as "otomycosis" without the slightest reference to how that diagnosis was established in any of the cases. Reference is made to a similar condition in which bacteriological examination showed among other things, "numerous unidentified large gram positive bacilli, frequently occurring in chains"; this was not to be confused with "otomycosis." It was further pointed out that the treatment suggested was not successful in combatting infection with *Aspergillus Niger* (the best recognized form of otomycosis). In view of the remarks made regarding these conditions, it appears that some bacteriologic or mycologic studies were made, but the author makes no mention of the results of such studies in the cases which he considered to be otomycosis about which the article is written and for which his treatment is effective.

Dermatologists in general are likely to be confused by the otologist's diagnosis of otomycosis, and this article serves to compound the confusion further. What type of otomycosis other than that due to *Aspergillus Niger* is recognized by otologists, what is the identity of the mycotic invader at fault and how is the diagnosis made? Perhaps it is diagnosed by "therapeutic test" with the "therapy of proved efficacy" suggested in the article to which I refer.

Yours very truly,  
A. FLETCHER HALL, M.D.

*This letter was forwarded to Dr. Bryant, whose reply appears in the adjoining column.*

Santa Monica

Editor,  
CALIFORNIA MEDICINE

Los Angeles

Dear Sir:

I have read the letter addressed to you by Dr. A. Fletcher Hall regarding my article, "A Therapy of Proved Efficacy in Otomycosis," which appeared in the May issue of CALIFORNIA MEDICINE.

In reply to Dr. Hall's statement that there was no reference in the article as to how the diagnosis was established, I refer him to the first paragraph of that portion of the paper headed, "Therapy of Otomycosis," and particularly to the last sentence of this paragraph, namely: "The appearance of the canal is so characteristic that, after some experience, it is unnecessary to make routine microscopical examinations, particularly since the fact that the treatment is universally effective obviates the necessity of identification of the various mycotic strains." I abide by this statement. Certainly, at the outset of this study routine microscopic examinations were made and revealed the various mycelial strains found in otomycosis. I certainly disagree with Dr. Hall's statement that infection with *Aspergillus Niger* is the best recognized form of otomycosis, and I feel that this subject is dealt with sufficiently in the paper.

As cases of this type were seen over and over again, it became necessary to make microscopical studies only in those cases which presented some unusual clinical feature, and I feel that this practice is not too different from that followed in general or dermatological work.

I regret exceedingly that my article "serves to compound the confusion further" for Dr. Hall. I can only say that the facts presented and the treatment outlined have served to clarify this problem for many otologists and general practitioners. The series of cases presented has been augmented by several hundred additional cases, the outcome of which has served to support the statements made.

Yours very truly,  
BEN L. BRYANT

# CALIFORNIA MEDICAL ASSOCIATION

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JOHN HUNTON	Executive Secretary		

## NOTICES AND REPORTS

### Your Medical Association

*In reply to a request by the Commissioner of Internal Revenue for information needed for a review of the tax-exempt status of the California Medical Association, the association's legal counsel has prepared and sent to the commissioner the following statement of the organization's purposes and activities.*

#### 1. STATEMENT OF ACTIVITIES

##### *Executive Offices:*

Executive offices of the Association are maintained at 450 Sutter Street, San Francisco, California, and 606 Subway Terminal Building, 417 South Hill Street, Los Angeles, California, for the purpose of administering and coordinating the activities of the Association and editing and compiling the monthly scientific publication of the Association known as CALIFORNIA MEDICINE. A full-time staff is employed, composed of: The Executive Secretary, Field Secretary, Assistant Executive Secretary, Editorial Assistant, Advertising Manager and five stenographers and clerks. The Editor of CALIFORNIA MEDICINE is a physician employed on a part-time basis to supervise the editing and publishing of the magazine. The Executive Secretary serves as business manager of the magazine. The amounts paid to employees of the Association during 1946 and 1947 are set forth in the statements of receipts and disbursements for said years that are attached hereto and made a part of this affidavit.

The policies which guide the executive and administrative staff are laid down by the House of Delegates of the Association, composed of slightly over two hundred physicians who are elected by their respective county medical societies; by the Council of the Association, which is the executive body and is composed of fifteen councilors plus the officers of the Association, all of whom are elected by the House of Delegates; and the officers of the Association, consisting of the president, president elect, speaker, vice speaker, and secretary-treasurer. All delegates, councilors and officers of the Association are physicians.

##### *California Medicine:*

One of the prime activities of the California Medical Association is to carry on a program of education

for the benefit of its members, at present approximately nine thousand four hundred doctors of medicine in the State of California. CALIFORNIA MEDICINE constitutes one of the chief media used by the Association to carry out this purpose. Each issue contains articles on scientific medicine, clinical medicine, medical research, and public health, together with news articles of interest to the medical profession and comments and editorials on the scientific, social and economic aspects of the practice of medicine. Copies are furnished all members without additional charge and as a part of their membership benefits. It is printed by a private printing firm, under contract with the Association. Most of the articles appearing in it are prepared by members of the Association or by physicians from other states. Copy is prepared or edited in the executive offices, where proof is read, mailing envelopes are addressed, and all circulation and advertising matters are handled. CALIFORNIA MEDICINE is not a profit-making project, as revenue derived from advertising has often covered only a portion of the cost of publication.

CALIFORNIA MEDICINE is published monthly, and representative copies of it are submitted herewith in accordance with the request contained in your letter of June 7, 1948.

##### *Cancer Commission:*

The Association maintains a Cancer Commission, composed of nine physicians who are members of the Association. It is the function of the Cancer Commission, which it has diligently carried out during the years in question, to stimulate and aid in the education of the public toward the understanding of cancer, to promote research leading toward development of means of alleviating or curing cancer, and to promote and stimulate dissemination of knowledge amongst practicing physicians with respect to methods and procedures for detecting and diagnosing cancer and treatment of same. The Cancer Commission of the California Medical Association has joined with the American Cancer Society and formed a California nonprofit charitable corporation, known as the American Cancer Society, California Division.

This corporation, managed jointly by the Cancer Commission of the California Medical Association and public-spirited citizens, commenced in 1945 an active campaign in California,

- (a) To educate the public to recognize symptoms that might indicate the presence of cancer and to seek early medical attention when such symptoms arise,
- (b) To stimulate and aid and assist in the establishment of consultative tumor boards, conducted without charge to the public,
- (c) To aid and assist in the care and treatment of needy persons having cancer.
- (d) To promote, aid and assist research in the field of cancer.

Prior to January, 1946, the Cancer Commission did not employ any full-time assistants. Since then, however, it has employed a physician as its medical director on a full-time basis. The medical director of the Cancer Commission also serves as medical director of the American Cancer Society, California Division, and his salary, costs and expenses are shared by this Association and the American Cancer Society, California Division.

#### *Postgraduate Study:*

The Association, through its standing committee on postgraduate activities, maintains throughout California an active program of postgraduate education of its members. Prior to 1947, the committee on postgraduate activities functioned through the employees in the executive offices. However, in 1947 a physician member of this Association was employed on a part-time basis to act as director of postgraduate activities, and in the latter part of 1947 a contract was entered into under which the duties of the director of postgraduate activities will become a full-time function. Conferences and meetings for postgraduate study have been arranged in various parts of California, and this work of the Association is carried on continuously.

#### *Physicians Benevolences:*

For the purpose of providing aid to aged physicians who are in financial need and to the families of members or former members of the Association who are in need, the Association maintains a committee on physicians benevolences. By action of the House of Delegates of the Association the sum of \$1 per member is irrevocably set aside each year out of the revenues of the Association for the physicians benevolences fund. This fund is used only for the purpose of granting financial assistance to needy physicians or to the families of needy physicians.

#### *Blood Bank Activities:*

The Association maintains a special committee on blood banks. This committee during the years 1945, 1946 and 1947 has cooperated and coordinated with the blood bank advisory committee of the California State Department of Public Health, and with blood banks maintained by several of the component county medical societies in California. The work of the blood bank committee has involved aid and as-

sistance in the entire field of collection, processing, and distribution of blood and blood plasma.

#### *Public Relations:*

As a part of its purposes, viz. to promote the science and art of medicine and to protect the public health, the Association during 1945, 1946 and 1947 carried on an active public relations program under the direction of its Council and Executive Committee. The purpose of this program was to acquaint the public with medical and public health facts, and to enlist the cooperation of the public in activities designed to maintain and improve the health of all citizens. Particularly, a public educational campaign was carried on to point out the benefits to the public of enrolling in accredited, approved and reputable health insurance programs. The public relations activities of the Association have been carried on in the following ways:

(a) Through the promotion in each community in California of a "voluntary health week" proclaimed by the mayor of the community, during which public meetings were arranged and speakers obtained for the purpose of acquainting the citizens of the community with the availability of voluntary health insurance plans and the desirability of protecting against the costs of medical care by purchasing health insurance contracts. There are fifty-eight counties in California, and during the years 1946 and 1947 voluntary health weeks were held in most of the counties. The Association maintained a special staff for the purpose of arranging and organizing voluntary health weeks, and this staff devoted its full time during the years 1946 and 1947 to the conduct of public health weeks.

(b) Through supplying speakers for meetings of lay groups and organizations on public health and medical subjects.

(c) Through a radio program sponsored by the Association, established in May, 1946 through the Mutual Broadcasting System, and in 1947 transferred to the American Broadcasting System. This radio program is entitled "California Caravan" and is a weekly program. Each week a historical drama portraying a significant historical event in California is presented, together with a statement on behalf of the Association advocating in the public interest that voluntary health insurance be obtained by California families. While the program does not limit itself to any one health insurance plan, emphasis is placed on California Physicians' Service, nonprofit California corporation in which almost all of the members of the Association are members and which on a nonprofit service basis offers medical, surgical and hospital care to the public on a prepayment basis (for the status of California Physicians' Service, see *California Physicians' Service v. Garrison*, 28 Cal. (2d) 790).

(d) Through newspaper releases on medical and health subjects.

(e) Through conferences and personal contacts with representatives of many organizations and groups.

*Public Policy and Legislation:*

The standing committee on public policy and legislation of the Association reviews legislative proposals pending in the California Legislature, analyzes these proposals, and through the publications of the Association and correspondence acquaints the individual members of the Association with the nature of such legislative proposals. Members of this committee and the officers of the Association supply members of the State Legislature with information on medical and health questions, and appear before committees of the Legislature and express the views and policies of the medical profession of California on pending legislative matters.

With respect to national legislative proposals affecting medicine and the public health, this Association does not carry on any direct activity. However, through its committee on public policy and legislation it maintains membership in The United Public Health League, a nonprofit association of medical societies and doctors of medicine in the eleven western states. The United Public Health League fulfills essentially the same functions with respect to the Congress that the committee on public policy and legislation of this Association fulfills with respect to the California Legislature.

*Hospital Construction:*

During the past several years there has been a shortage of hospital beds in California, and through state and federal legislation the California State Department of Public Health has been designated as the state agency, having charge of new hospital construction, and has federal and state grants to dispense to new hospital projects. Officers and employees of the Association have served on advisory committees with the State Department of Public Health, on special committees of the State Chamber of Commerce, and the Association itself, through its executive officers, has acted as a clearing house for information concerning new hospital construction. The activities of the Association in this field have consumed a great deal of time of the officers and employees of the Association, and have had as their object and purpose the correlation and promotion of needed hospital construction in this state.

*Placing Physicians:*

The Association maintains a placement service for physicians seeking locations in California and for physicians, hospitals, communities or others seeking medical services. This service is provided without charge to either the physician seeking placement or those seeking medical services. It is of particular use and advantage to small rural communities where the provision of medical care is more of a problem because of greater distances, sparser population and inferior equipment available to the practicing physician. This service is available to all physicians, regardless of their membership status in the Association, and to all communities, civic organizations, hospitals or others. It functions throughout the year and has been successful in placing numerous physi-

cians in areas where their services are of benefit to the community and the public health.

*Industrial Practice:*

Through the standing committee on industrial practice and the executive officers of the Association, the Association has cooperated with the State Industrial Accident Commission in the establishment and maintenance of minimum fee schedules for physicians performing services that fall within the California Workmen's Compensation law. During 1945 and 1946 the Executive Secretary of the Association served on a special study committee appointed by the Industrial Accident Commission to study the entire field of payment for medical services under the Workmen's Compensation law. In 1942 the Association itself filed and presented to the Industrial Accident Commission a petition for the establishment of a new minimum fee schedule. Several public hearings were held, at which the Association appeared on behalf of its members. In November, 1946, a new fee schedule was adopted. Since November, 1946, the Association has been active in conferences, and consultations with the Industrial Accident Commission, interested insurance companies, and others, in order to protect and maintain the minimum fee schedule for medical services rendered under the California Workmen's Compensation law.

*Annual Session:*

Once each year the Association holds an annual meeting to which the entire membership of the Association is invited. The meeting customarily lasts for four days. Scientific and technical exhibits are available for the members. The annual session is divided into two parts: the scientific assembly and the House of Delegates. The scientific assembly consists of all of the members of the Association and is divided into sections, each section representing a medical specialty. Each section holds meetings at which papers are presented and discussed relating to recent scientific advances in the particular specialty. General meetings of the entire scientific assembly are held, and customarily guest speakers of national prominence in medical fields are invited to present papers to the general assembly and the specialty sections. The House of Delegates, which meets during the annual session is, as previously stated, the legislative body of the Association. Regular annual meetings were held in 1945, 1946 and 1947. One of the issues of CALIFORNIA MEDICINE attached hereto contains the "Pre-Convention bulletin" for the 1947 annual meeting, and from it the nature and extent of the scientific program at the annual session may be ascertained.

*Miscellaneous Activities:*

In addition to carrying on routine duties and handling correspondence from members on a variety of subjects, the officers and employees of the Association represent the Association at meetings of various groups and agencies and maintain contacts with governmental agencies administering public health and other programs related to the practice of

medicine, in order that there may be maintained a proper coordination between such activities and the members of the medical profession. The miscellaneous activities of the Association, through its officers and employees, encompass such a tremendous volume of work that it is impractical to detail each activity. The following, however, are examples of these miscellaneous activities: Maintenance and furnishing of data on availability of hospital services and health insurance plans, medical schools, physicians who are certified specialists, institutions providing specialized care for the mentally ill, vital statistics, and many other like services.

#### II. DUES AND DUES-PAYING MEMBERS

The rate of dues in effect during each of the years 1945, 1946 and 1947 and 1948, and the number of dues-paying members each year are as follows:

Year	Dues	Dues-paying Members
1945.....	\$ 20	6108
1946.....	\$100	7528
1947.....	\$100	8675
1948.....	\$ 60	8699

During 1945 and to some extent in 1946, the number of dues-paying members was considerably less than the total active membership of the Association, because during the war years dues were waived entirely for all active members serving in the armed forces. As a consequence of the waiver of dues for military service which was effective during the years 1942 to 1946, inclusive, the revenues of the Association were considerably reduced under the normal prewar years.

#### North Bay Postgraduate Seminar

Benign Gastro-Intestinal Disease was the subject of a full day seminar held by the California Medical Association Postgraduate Committee at Santa Rosa, June 18, for the five north bay counties of Sonoma, Marin, Napa, Lake and Mendocino. A faculty of four teachers from San Francisco presented the material. Two cases presented at the morning Clinical Conference Session by the Staff of the Sonoma County Hospital provided a practical basis for discussion of ulcerative colitis and peptic ulcer.

#### PROGRAM

10:00 A.M.-12:00 Clinical Conference  
 1:30 X-Ray Diagnosis of Peptic Ulcer—Ivan J. Miller, M.D.  
 2:30 Peptic Ulcer, Clinical Diagnosis and Medical Management—Hugh Rose, M.D.  
 3:30 Peptic Ulcer, Recent Advances in Surgical Treatment—Roy Cohn, M.D.  
 4:30 Motion Picture: "Subtotal Gastrectomy for Perforating Duodenal Ulcer."  
 7:00 Dinner and Evening Session.  
 8:00 Non-Surgical Diseases of the Colon—Hugh Rose, M.D.  
 8:30 Surgery of the Colon—Victor Richards, M.D.

Doctor Ivan Miller, radiologist, emphasized the importance of careful evaluation of x-ray films in

diagnosis of peptic ulcer, pointing out the factors leading to errors in diagnosis. He advocated examination of the patient without a preliminary barium meal, and urged that no gastric analysis or other irritating procedures be carried out immediately before x-ray examination. Gastric and duodenal herniae, hiatal hernia and colon lesions were discussed and illustrated by representative films. The speaker stressed the difficulties in the x-ray diagnosis of ulcerative colitis but pointed out the importance of the characteristic "granular mucosal pattern in a tubular appearing colon."

Dr. Hugh Rose, Jr., discussed the diagnosis and treatment of peptic ulcer. He emphasized the fallacy of relying too much upon the history, as in only 17 per cent of cases in which the diagnosis has been proven have the patients had a history classically indicative of the disease. Gastric analysis, x-ray and gastroscopy are important adjuncts in arriving at an accurate diagnosis, but each has its limitations, Dr. Rose said. It is therefore necessary to evaluate carefully the results of all available means of diagnosis and to supplement by repeated examinations. Treatment, the speaker said, is based upon proper balancing of the acid-base equilibrium, frequent feeding of easily assimilable foods, and inhibition of the pepsin activity through avoiding roughage, condiments and alcohol except in diluted forms. Dr. Rose also discussed the recent work done on an ulcer preventing factor, Vitamin "U," found in vegetable juices, particularly cabbage. The addition of adequate amounts of the raw juice to the diets was followed by a definite improvement in the rate of healing of experimentally produced ulcers in animals and of ulcers in a small series of patients.

Dr. Roy Cohn outlined the important factors in surgical procedures of the esophagus and stomach. He pointed out the recent reduction in surgical mortality in patients operated upon for ulceration of the lower one-third of the esophagus. As to gastric ulcer, he said that inasmuch as 14 per cent of demonstrable gastric ulcers are malignant, surgical resection should be considered for any lesion of the stomach that does not heal after four weeks of adequate medical treatment. He also reviewed the physiological aspects of vagotomy, pointed out the difficulties presented by the 20 per cent of patients having diffuse vagal trunks, and called attention to the poor results accruing from a combination vagotomy and resection. The two entities most amenable to vagotomy are marginal ulcer and gastro-jejunocolic fistula, the speaker said. The indications for gastric resection, he said, are symptoms of obstruction and persistent or repeated hemorrhage. A careful evaluation of the patient must be made, with his age especially considered, as patients over 50 years of age are much more prone to exsanguinate. In the presence of massive gastric hemorrhage, a patient should receive 1000 cc. of whole blood immediately on diagnosis of the emergency. In case of persistent bleeding the patient should be explored immediately while receiving continuous blood transfusions for replacement of blood lost.

Dr. Cohn also discussed the treatment of hiatal hernia of the stomach. Calling attention to the relatively high incidence of recurrence following the usual types of operation, he briefly outlined the technique of herniotomy and repair by suture of the wall of the stomach to the diaphragm. This is a relatively simple procedure, he said, and as to the rate of recurrence, most satisfactory. Postoperative care, as outlined by the speaker, consists of maintaining gastric suction until restoration of peristalsis and relative healing of the anastomosis is established, ambulation on the first or second day postoperatively, fluid and electrolyte balance maintenance according to the patient's condition to insure a urinary output of 1000 cc. and 4 to 5 gm. of urinary chlorides which may be easily evaluated by use of a simple colorimetric test for chloride. Penicillin is given, 40,000 units every three hours. Amino acids are not given parenterally, although oral administration is started early. Plasma is not considered physiological and, because of the danger of homologous serum jaundice, is not given.

In discussing the diagnosis of diseases of the colon Dr. Rose pointed out the common characteristic of vagueness of symptoms, the unreliability of results of single laboratory procedures, the advantage of air-contrast x-ray films of the colon, the necessity of proctoscopic and sigmoidoscopic examinations which provide a means for direct visual examination, for culture of ulcerative lesions and for biopsy. He stressed the importance of early surgical consultation in cases of ulcerative colitis resistant to medical treatment, in order to prevent the establishment of an irreversible chronic state. A hopeful recent development in the therapy of this disease, the speaker said, is the oral use of whole duodenal substance. Reports of this work have not been published, but communications regarding progress of reliable research are very encouraging, he said.

Dr. Victor Richards, discussing surgical operations on the colon, pointed out that, due to the sensory innervation, tenesmus is characteristic of lesions of the ano-rectal region, while obstruction is indicative of lesions in the sigmoid and transverse colon, and bleeding, anemia and loss of weight suggest the right colon as the site of malignant disease. The complications of obstruction, infection from perforation, fistulae, and hemorrhage were reviewed. The speaker outlined the surgical management of ulcerative colitis for the restoration of water, electrolyte and physiological equilibrium by ileostomy maintained for a period of one to four years or permanently, or resection of the colon in stages, with eventual ileorectal anastomosis. In the latter connection he reported on the experimental work done at Johns Hopkins of bringing the terminal ileum through the anal sphincter, and on Dennis' work in Minnesota using vagotomy in ulcerative colitis for relief of the spasms and resultant vicious cycle.

A total of 43 physicians attended the seminar from the five counties. The afternoon session was best attended, with 39 present. At the evening session the attendance was 26, and at the morning session, 18.

The attendance from counties other than Sonoma was very light, with three each from Marin and Napa, and one each from Lake and Mendocino.

### Announcement

#### Stanford University School of Medicine Postgraduate Courses for Practicing Physicians

September 6-10, 1948

Registration closes August 16, 1948. Fee \$50.00 (Not covered by veterans' educational benefits.) Apply to Dean, Stanford University School of Medicine, 2398 Sacramento Street, San Francisco 15, California.

#### Morning Courses, Monday through Friday, 8:30-12

- Course 1. Surgical Emergencies and Fractures.
- Course 2. Internal Medicine.
- Course 3. Obstetrics and Gynecology.
- Course 4. Psychosomatic Problems in Patients with Organic Disease.

#### Afternoon Courses, Monday through Friday, 1:30-5

- Course 5. Cardiovascular Diseases.
- Course 6. Proctology.
- Course 7. Diseases of the Chest.
- Course 8. Problems in Pediatrics.

### GENERAL MEETINGS

Lane Hall—8 to 10 P.M.

Tuesday: Behavior Problems in Pediatrics, Dr. Hale F. Shirley.

Wednesday: Radioactive Isotopes in Medicine, Dr. R. R. Newell.

### Council Meeting Minutes

#### Tentative Draft: Minutes of the 354th Meeting of the Council

Los Angeles, California, June 5-6, 1948.

The meeting was called to order by Chairman Bruck at 10 a.m., Saturday, June 5, 1948, in Conference Room No. 5 of the Biltmore Hotel, Los Angeles.

#### 1. Roll Call:

Present were President Askey, President-Elect Kneeshaw, Vice-Speaker Charnock, Councilors Ball, Crane, Henderson, Anderson, Ray, Bruck, Lum, Pollock, Cherry, MacLean, Hoffman, Shipman, and Bailey, Secretary Garland and Editor Wilbur.

Absent: Speaker Alesen (illness); Councilors Green and Thompson (attending conflicting meetings).

Present by invitation were Dr. Dwight H. Murray, Chairman of the Committee on Public Policy and Legislation; Executive Secretary Hunton, Assistant Executive Secretary Wheeler; Legal Counsel Hassard; Public Relations Counsel Clem Whitaker; Mr. William M. Bowman, Executive Director of Cali-

fornia Physicians' Service; Mr. Ed Clancy of the Los Angeles office, Mr. Ben H. Read, Executive Secretary of the Public Health League of California, and county society executive secretaries Venables of Kern County, Donovan of Santa Clara County, Kihm of San Francisco County and Waterson of Alameda County.

Present by invitation during portions of the meeting were Dr. William L. Bender, Chairman of the Council's Committee on C.P.S. Fee Schedule, Dr. Paul Tully of the Association of Santa Fe Coast Lines Physicians' Association, and Drs. Forrest Gruningen and C. E. Atkins, representing the California Osteopathic Association.

#### 2. Minutes:

(a) On motion duly made and seconded, the minutes of the 349th to 353rd meetings of the Council, held daily from April 10 to April 14, 1948, inclusive, were approved.

(b) On motions duly made and seconded, minutes of the 208th and 209th meetings of the Executive Committee, held April 14 and May 9, 1948, were approved.

#### 3. Appointment of Field Secretary:

Following approval of the minutes of the May 9, 1948, meeting of the Executive Committee, in which approval had been given for locating the Association's Southern California office in Los Angeles, it was regularly moved, seconded and voted that Mr. Ed Clancy, Southern California representative, be given the title of Field Secretary.

#### 4. Membership:

(a) A report of membership as of June 3, 1948, was received and ordered filed.

(b) On motion duly made and seconded, three 1947 delinquent members whose 1947 dues had been received since the last previous Council meeting, were ordered reinstated to active membership.

(c) On motion duly made and seconded, two hundred thirteen (213) members whose 1948 dues had been received since the last previous Council meeting were ordered reinstated to active membership.

(d) On motion duly made and seconded in each instance, three applicants for Associate Membership were granted Associate Membership. These were: Herman Nussbaum and Ruth A. Pillsbury of Alameda County, and Edmond V. Minasian of Yuba-Sutter-Colusa County.

(e) On motions duly made and seconded in each instance, the following sixteen (16) members were voted Retired Membership:

John Ohanneson, Alameda County.  
H. A. Jacobson, Fresno County.  
John H. Breyer, Los Angeles County.  
G. Sherman Clark, Los Angeles County.  
Glenn G. English, Los Angeles County.  
William E. Hart, Los Angeles County.  
Roscoe M. Nicholson, Los Angeles County.  
Charles Edward Remaly, Los Angeles County.  
Roy N. Taylor, Los Angeles County.

A. C. Willmott, Los Angeles County.  
Henry W. Gibbons, Sacramento County.  
Robert G. Pearson, Sacramento County.  
Clarence E. Hyde, San Francisco County.  
Hermon F. Wilson, San Francisco County  
E. W. Mullen, Santa Clara County.  
George H. Runckel, Siskiyou County.

(f) On motions duly made and seconded in each instance, Life Membership was voted for the following four applicants:

William J. Quinn, Humboldt County.  
Martin G. Carter, Los Angeles County.  
F. W. Rinkenberger, Los Angeles County.  
Frank Krull, Sacramento County.

(g) The application of Dr. Deon A. Crew of San Luis Obispo for reconsideration of his earlier application for election to Life Membership was reviewed and it was agreed that such application would have to be made on the basis of existing provisions of the Constitution. It was regularly moved, seconded and voted that Dr. Crew be notified of the availability of Retired Membership in his case.

#### 5. Financial:

(a) Reports showing bank balances as of June 3, 1948, balance sheet as of May 31, 1948, and receipts and expenditures for May and for the eleven months ended May 31, 1948, were received and approved.

(b) On motion duly made and seconded, it was voted that a Council committee investigate the possibility of the short-term investment of Association funds currently held. Doctors Kneeshaw and Ray were named by the Chairman as members of this committee.

#### 6. Referee for County Medical Society:

A request was read from the Alameda County Medical Association that the Council appoint a referee to preside over the hearing of charges of unprofessional conduct brought against a member of that association. In accordance with the terms of Chapter 2, Section 3(a) (6) of the Association's By-Laws, the Council, on motion duly made and seconded, voted unanimously to appoint such a referee, the Executive Committee to select the referee as early as possible before the date of September 16, 1948, set for the hearing of the charges.

#### 7. A.M.A. "Grass Roots" Conference:

After discussion of the conference of County Society Officers ("Grass Roots" Conference) of the A.M.A., it was regularly moved, seconded and voted that Dr. J. Frank Doughty of Tracy be asked to represent the Association at the conference of June 20, 1948.

#### 8. Public Relations:

Mr. Whitaker reported on statements released to the press by State Insurance Commissioner Downey, in which critical comment was made on the activities of purveyors of voluntary forms of health insurance which tended to throw California Physician's Service into a false light. It was regularly moved, seconded

and voted that a letter sent by Mr. Hassard to Mr. Harold Haas, Deputy Attorney General representing the Insurance Commissioner, be approved and that Mr. Whitaker be authorized to take such steps as may be deemed necessary to counteract this type of statement.

**9. California Physicians' Service:**

Dr. Lewis T. Bullock appeared before the Council to suggest that certain changes be effected in C.P.S. fee schedules as they affect internists. He proposed that a committee of internists be appointed to meet with representatives of C.P.S. to this end. Dr. William L. Bender, Chairman of the Council's Committee on C.P.S. Fee Schedule, presented suggestions for changing certain sections of the existing fee schedule. Secretary Garland suggested that C.P.S. (1) establish a dual schedule of x-ray fees for specialists and general practitioners, (2) pay hospitals the same fees for x-rays as are paid to physician members of C.P.S. and (3) place an annual limit of a suggested \$25 or \$30 on the amount of x-ray services allowed beneficiary members.

Mr. Bowman presented the financial report of C.P.S. for April, 1948, pointing to an increasing balance in the unit stabilization (surplus) fund and an improved operating experience under present dues schedules and operating procedures.

Dr. Bender presented a tabulation of suggested fee schedule changes. On motion duly made and seconded, it was voted not to approve these suggested changes. It was regularly moved, seconded and voted that the Council give its C.P.S. Fee Schedule Committee full authority to proceed with a *complete revision of the present fee schedule*, the Council to recommend to the C.P.S. Board of Trustees that full consideration be given such suggestions.

It was regularly moved, seconded and voted that the Council request the C.P.S. Board of Trustees to establish a board of review to consider cases of apparent inequities among individual physician members of C.P.S.

**10. Association of Santa Fe Coast Lines Physicians:**

Mr. Hassard reviewed the status of the application of the Association of Santa Fe Coast Lines Physicians for adjudication of their demands on the Board of Directors of the Santa Fe Hospital Association for adjustment of compensation and other matters. He reported that the American Medical Association had not provided a representative for the Santa Fe physicians at the hearing of this matter before the National Railway Labor Board. Dr. Paul Tully, who appeared at this hearing, reported on the nature of the proceedings.

It was regularly moved, seconded and voted that Dr. Tully be reimbursed in the amount of \$300 for the expenses of his trip to Chicago to make this appearance. It was regularly moved, seconded and voted that Dr. Dwight H. Murray bring before the Board of Trustees of the American Medical Association the displeasure of the Association at the A.M.A.'s failure to provide representation for Dr. Tully.

**11. Committee on Industrial Practice:**

Dr. Donald Cass, Chairman of the Committee on Industrial Practice, reported to the Council that the Industrial Accident Commission of the State of California had scheduled hearings for June 7 in Los Angeles and June 10 in San Francisco on an application of the Western Orthopedic Association for a review of certain of the items in the present schedule of industrial medical fees. Dr. Cass stated that his committee had nearly completed its work on a proposed revision of the fee schedule and suggested that the Association appear at these hearings and make such a report to the Commission. On motion duly made and seconded, it was voted to approve this type of presentation to the Industrial Accident Commission, the Association to be represented by Dr. Cass, Messrs. Hassard and Hunton, and Hon. Sam L. Collins, associate legal counsel.

Dr. Cass also reported that he had been in touch with Dr. Christopher Leggo, Chairman of the special Committee on Industrial Health, and that the two committees planned to meet in order to delineate the areas of responsibility of the two.

**12. Recess:**

At this point, 5:45 p.m., the Council recessed until 9 a.m., Sunday, June 6, 1948.

**13. Reconvention:**

The Council reconvened in the same room at 9 a.m., Sunday, June 6, 1948.

**14. Roll Call:**

On roll call, all those noted present June 5 were present, with the exception of Councilor Bailey, absent at a Board of Medical Examiners meeting. Also present was Councilor Thompson. Present by invitation was Dr. Wilton L. Halverson, State Director of Public Health.

**15. California Medicine:**

Editor Dwight L. Wilbur of CALIFORNIA MEDICINE reported that Dr. Hamilton Anderson had tendered his resignation from the advertising committee of the publication and that Dr. Nelson Howard had been compelled to resign from the committee for health reasons. He suggested that the interim appointment of Dr. John W. Cline to succeed Dr. Howard be confirmed and that the committee avail itself of the services of Dr. R. W. Weilerstein of the Federal Food & Drug Administration and call upon Doctors Hamilton Anderson, Paul Hanzlik and C. H. Thienes as consultants in pharmacology. On motion duly made and seconded, these suggestions were voted approval.

Dr. Wilbur also outlined a proposal received from staff members of the University of Chicago to publish an annual review of medical progress, to be offered to readers of CALIFORNIA MEDICINE as a supplement or as a separate publication at a cost subscription rate. After discussion, it was regularly moved, seconded and voted that this review be made available to readers of CALIFORNIA MEDICINE on a voluntary basis if that is practicable.

**16. California Society of Allergy:**

Attention was called to the formation of the California Society of Allergy, which carries on its letter-head the phrase "A Section of the California Medical Association." It was pointed out that the 1948 House of Delegates had established a section on allergy but that this section was not empowered to adopt a separate society name. On motion duly made and seconded, it was voted that the Secretary notify the allergy society on this point and also advise the Bulletin of the Los Angeles County Medical Association, which had printed a letter from this society, that there was an ambiguity of titles involved in this situation.

**17. Palo Alto Clinic:**

A letter from a Palo Alto physician, calling attention to alleged defects in the contract for health care recently adopted by the Palo Alto Clinic and the Menlo School and Junior College, was read and it was agreed that no Council action was required since the contract had already been approved by the two county medical societies involved.

Further discussion was had on the advisability of notifying students of the availability of voluntary forms of medical care insurance and it was agreed the Secretary should take up with the Committee on Health and Public Instruction the matter of presenting to college students suitable material along these lines.

**18. Blood Banks:**

The Chairman read a report from Dr. John R. Upton, chairman of the blood bank commission, outlining the activities of the commission in the past two months. No action required.

**19. 1948 House of Delegates:**

Discussion was held on various decisions of the 1948 House of Delegates which required Council action to put into effect.

(a) In regard to the amendment to Section 1, Article XI, of the Constitution, providing for reduction or waiver of dues in special cases, it was regularly moved, seconded and voted that subsection (b) of this section be governed by the words "War Service" in the title in order to provide a waiver of dues for members in military service.

(b) In regard to the reduction of dues in special cases (subsection (c) ) it was regularly moved, seconded and voted that a committee of three Council members prepare schedules of recommended dues and report back to the Council. The chairman named Dr. Kneeshaw as chairman of this committee, Doctors Charnock and Anderson as members.

(c) In regard to subsection (g) of Section 1, Article XI, it was regularly moved, seconded and voted that minimum dues of \$3 per year be applied to all eligible membership classes mentioned in the section and that the Secretary notify the county medical societies that such classes of membership are now available.

(d) In regard to Resolution No. 8, relative to additional training and teaching facilities, it was regularly moved, seconded and voted that the deans of

the five medical schools of California, or their representatives, be appointed a committee to study this problem.

(e) In regard to Resolution No. 10, relative to corporate practice of medicine, it was regularly moved, seconded and voted that the Council appoint a committee to study this matter and report back to the Council prior to its first meeting in 1949. The chairman, with the consent of the Council, named Dr. Wilbur Bailey as chairman of this committee, with Doctors Dell Lundquist, Russel V. Lee, Lewis T. Bullock, and Robert Blackmun as members.

(f) In regard to Resolution No. 11, relative to compensation of physicians in tax-exempt hospitals, it was regularly moved, seconded and voted that the resolution be referred to the Committee on Public Policy and Legislation, with the request that this committee seek the assistance of the Association of California Hospitals in taking the required legislative steps to correct present inequities.

(g) In regard to Resolution No. 14, relative to wider choice of physicians by injured workmen, it was regularly moved, seconded and voted that the matter be referred to the Committee on Industrial Practice, with the request that the committee confer with Dr. F. J. Gaspard of Los Angeles, maker of the original resolution.

(h) In regard to Resolution No. 21, relative to the system of coroners' examinations, it was regularly moved, seconded and voted that this subject be referred to the Committee on Public Policy and Legislation.

(i) In regard to Resolution No. 23, relative to operation of the Crippled Children's Act, it was regularly moved, seconded and voted that the Executive Committee confer with the State Director of Public Health in order to clarify the situation.

(j) In regard to Resolution No. 24, relative to mental hygiene clinics, it was regularly moved, seconded and voted that the legislation authorizing the establishment of mental hygiene clinics be investigated.

(k) In regard to Resolution No. 26, relative to payment by California Physicians' Service for radiological services in hospitals, it was regularly moved, seconded and voted that copies of this resolution be sent to all hospitals in California.

**20. Hospital Construction:**

The Council discussed a proposed statement which outlined the various types of hospitals which might be built in California, the sources of funds available for each type and the advantages and disadvantages of the several types of financing. It was regularly moved, seconded and voted that this statement be adopted as presented and that copies of it be sent to all component county societies, together with an explanatory letter.

**21. State Department of Public Health:**

Dr. Wilton L. Halverson, State Director of Public Health, discussed the publication by his department of a list of 198 proposed "health centers" and pointed out that this list represented an ideal distribution of

centers for the use of local health authorities and was not actually a plan of his department. He also discussed the allocation of hospital construction funds, state and federal, which is under the jurisdiction of his department, and stated that the representatives of the State Department of Public Health were not campaigning for or against any specific type of hospital.

**22. California Society for Crippled Children:**

Mrs. Fred Markham and Mrs. E. E. Smith appeared before the Council and presented the proposed program of the California Society for Crippled Children for establishment of a program to detect and control epilepsy. They stressed the fact they wished to work with the physicians and the county or local medical societies. After discussion, it was regularly moved, seconded and voted that the Council Chairman prepare a set of standards to apply to this program and report back to the Council.

**23. Fee for Legal Services:**

Mr. Hassard presented a statement for extraordinary legal services, as approved by the Council and House of Delegates in establishing the budget, in the amount of \$2,000. On motion duly made and seconded, this statement was approved for payment.

**24. California Joint Committee on School Health:**

An invitation for the Association to be represented at the June 21-July 9 session of the California Joint Committee on School Health, sponsored by the State Department of Education, was approved and the chairman authorized to name a representative for this conference.

**25. Emblems for Members of 50-Year Standing:**

The Executive Secretary reported that the Association's records of membership do not extend back fifty years and, accordingly, no members' names were available for distribution of 50-year membership emblems as approved by the House of Delegates. It was agreed that the records of the county medical societies would be accepted for this purpose.

**26. National Health Assembly:**

A resolution adopted by the Council of the Utah State Medical Association, criticising the appropriation of funds by the American National Red Cross and other organizations which rely on publicly-contributed funds, for purposes of promoting the National Health Assembly, was approved in principle and the California Delegates to the A.M.A. authorized to support such a resolution in the A.M.A. House of Delegates.

**27. Ethics in Eyeglass Dispensing:**

A letter was read from a member in Fresno, outlining several methods proposed for the dispensing of eyeglasses in an ethical manner. It was agreed that the best solution presented was the encouragement of additional optical companies to locate in the area.

**28. Pathological Laboratory:**

A letter was read from a member seeking an opinion on the incorporation of a pathological laboratory

to serve the physicians of his community. It was regularly moved, seconded and voted that the member be advised that the incorporation of such a laboratory presented ethical considerations which might best be met by the physician operating his own laboratory without forming a corporate structure.

**29. Time and Place of Next Meeting:**

It was agreed that the next meeting of the Council should be held in San Francisco on August 21 and 22, 1948.

Adjournment.

L. HENRY GARLAND, M.D., *Secretary*

EDWIN L. BRUCK, M.D., *Chairman*

**In Memoriam**

DAVIS, JOSEPH PAUL, JR. Died in Turlock, May 20, 1948, age 33, of a heart attack. Graduate of the University of Oklahoma School of Medicine, Oklahoma City, 1942. Licensed in California in 1943. Doctor Davis was a member of the Stanislaus County Medical Society, and the California Medical Association.

OGDEN, JAMES CHESTON. Died in Long Beach, May 25, 1948, age 45, of injuries suffered in a fall from the roof of his apartment house. Graduate of the State University of Iowa College of Medicine, Iowa City, 1930. Licensed in California in 1937. Doctor Ogden was a member of the Los Angeles County Medical Association, the California Medical Association, and Fellow of the American Medical Association.

REISS, OSCAR. Died in Beverly Hills, June 17, 1948, age 65, of coronary thrombosis. Graduate of the University of Illinois College of Medicine, Chicago, 1906. Licensed in California in 1913. Doctor Reiss was a member of the Los Angeles County Medical Association, the California Medical Association, and a Fellow of the American Medical Association.

SCHURMEIER, HARRY LEACH. Died in Santa Barbara, May 12, 1948, age 65, of a myocardial infarction. Graduate of Northwestern University Medical School, Chicago, Illinois, 1911. Licensed in California in 1913. Doctor Schurmeier was a member of the Santa Barbara County Medical Society, the California Medical Association, and a Fellow of the American Medical Association.

SNURE, HENRY. Died in Los Angeles, May 17, 1948, age 71. Graduate of the University of Louisville School of Medicine, Kentucky, 1910. Licensed in California in 1916. Dr. Snure was a retired member of the Los Angeles County Medical Association and the California Medical Association.

WALKER, CALVIN ALBERT. Died in San Francisco, May 18, 1948, age 73, of a heart attack. Graduate of the Cooper Medical College, San Francisco, 1905. Licensed in California in 1905. Dr. Walker was a member of the San Francisco County Medical Society, the California Medical Association, and a Fellow of the American Medical Association.

WALSH, JOSEPH FRANCIS. Died in Eureka, May 28, 1948, age 63, of a heart ailment. Graduate of the Cooper Medical College, San Francisco, 1909. Licensed in California in 1909. Doctor Walsh was a member of the Humboldt County Medical Society, the California Medical Association, and a Fellow of the American Medical Association.

# NEWS and NOTES

NATIONAL • STATE • COUNTY

## ALAMEDA

Announcement of the award of a \$300 nurses' training scholarship to Shirley Van Ness, a student at Castlemont High School, was made recently by the Woman's Auxiliary to the Alameda County Medical Association. The scholarship was offered by the auxiliary as a part of its intensive program to stimulate interest in nursing as a profession. In an effort to help overcome the shortage of nurses, the auxiliary has also sponsored a poster contest in Alameda County schools to emphasize the attractiveness of nursing, and has arranged for speakers to address girls of high school age on the subject.

## CONTRA COSTA

In the June issue of *CALIFORNIA MEDICINE* it was erroneously reported that Dr. Edwin W. Merrithew was to retire as county health director on July 1. Actually his retirement was from the position of county physician and medical director of the county hospital. He did not serve as county health director.

## DEL NORTE

The Humboldt County Health Department has extended its service to Del Norte County under an agreement with the board of supervisors of the latter. The agreement provides that the Humboldt department will extend its facilities to Del Norte County, which will pay a percentage of the expenses based on county population. Dr. Kenneth W. Haworth, with headquarters in Eureka, will serve as physician for both counties.

## LOS ANGELES

Sharing in new grants-in-aid totalling \$16,000 awarded by the National Vitamin Foundation to support researches, is the University of Southern California Medical School. The grant is to assist Dr. E. Geiger, professor of pharmacology and toxicology, in investigations to determine the effects of time elements on the utilization of water soluble vitamins.

The mid-winter conference on Microscopic Tumor Pathology will be held Sunday, November 21, at the Los Angeles County General Hospital. Dr. A. Purdy Stout, Columbia University College of Physicians and Surgeons, will be chairman of the conference, and Dr. Louisa Keasbey, secretary. Dr. Keasbey will contact pathologists in California for cases for the conference. Reservations should be made with her at 1200 North State Street, Los Angeles 33.

Dr. Stout will also appear on the program of the refresher course at the Los Angeles County General Hospital on November 22-23. Dr. Justin Stein, 1407 South Hope Street in Los Angeles, is chairman of the committee that will have charge of the arrangements for the refresher course.

## MERCED

The City of Los Banos in Merced County recently made arrangements to have its public health service requirements taken over by the County Health department. Formerly the town had its own health service under the supervision of Dr. L. R. Hillyer.

## SAN BERNARDINO

The City of San Bernardino has set up a full-time health department with Dr. Warren Fox, formerly health officer of Riverside County, as director. Until the department began operating on a full-time basis, Dr. Finnis E. Wiggins was part-time health officer for the city. Dr. Robert S. Westphal, former deputy city health officer of Rochester, N. Y., has been appointed to the county post vacated by Dr. Fox.

## SAN FRANCISCO

A gift of \$41,000 for a fellowship in ophthalmology has been received by Stanford University from Upsilon chapter of the Delta Gamma sorority. Mrs. David Packard, president of the Stanford Delta Gamma Association, said that the money represented proceeds of the sale of the sorority house following dissolution of Stanford sororities in 1944.

Dr. Emile Holman, professor of surgery at Stanford University Medical School, was elected second vice-president of the American Surgical Association at a recent meeting.

With the opening of a ward for patients offering themselves for research in cancer in the Laguna Honda Home operated by the San Francisco Health Department, the University of California Laboratory for Experimental Oncology has gone into full operation.

A four point program of the laboratory includes the study of electronic characteristics of normal and malignant growth; investigation of the nature of changes in the whole body brought about by cancer; the experimental chemical treatment of cancer with new agents; and a fundamental study of the characteristics of human malignant tissue. Work at the laboratory is under the direction of Dr. Michael Shimkin, professor of experimental oncology, and he is assisted by Dr. Howard R. Bierman, associate professor of experimental oncology.

The laboratory is a cooperative venture of the University's Medical School and the National Cancer Institute, financed by the U. S. Public Health Service. It was established in January, 1947.

## STANISLAUS

A report on findings in gynecological researches was given by Dr. Daniel G. Morton, associate professor of gynecology at the University of California Medical School, at a recent meeting of the Stanislaus County Medical Society in Modesto. In a business session at the same meeting, Dr. Richard Husband was appointed as the society's advisor to the Omega Nu sorority to assist the sorority in the distribution of funds its has collected to aid handicapped persons in the community.

## TEHAMA

Dr. James Faulkner recently replaced Dr. O. T. Wood as health officer for the City of Red Bluff.

## GENERAL

Among appropriations for the University of California building program by the 1948 legislature were \$500,000 for

a virus laboratory at Berkeley and a \$5,000,000 for Medical School expansion at Los Angeles.

The 16th annual meeting of the Central Association of Obstetricians and Gynecologists will be held in Denver, September 23, 24 and 25, 1948.

The first annual meeting of the American Association of Blood Banks will be held August 26, 27, and 28, at the Hotel Statler, Buffalo, N. Y. Further information may be obtained from the office of the secretary, 3301 Junius Street, Dallas 1, Texas.

The Surgeon General of the Navy has announced the expansion of the professional training program for reserve and regular medical officers to permit more Navy doctors to meet the requirements of certification by the various American Specialty Boards, and to encourage the young doctor to intern under the auspices of the Navy. Graduates of Class A medical schools who have been accepted for internship by a hospital approved for such training by the Council on Medical Education and Hospitals of the A.M.A. may be commissioned as Lieutenants (junior grade) and permitted to continue their intern training. After completing their internships, the medical officers must remain on active duty for a period of one year. If they meet the professional, physical and moral requirements, they will be encouraged to transfer to the regular Navy.

Resident physicians now in civilian hospitals, or those accepted for approved residency training, are eligible for commissions in the regular Navy. Those so commissioned will be assigned to duty, with full pay and allowances, in the hospital in which they are already a resident or to which they have been accepted for residency training.

Information concerning any part of the program may be obtained by writing to the Chief of the Bureau of Medicine and Surgery, Navy Department, Washington 25, D. C.

The American Congress of Physical Medicine will hold its 26th annual scientific and clinical session September 7, 8, 9, 10 and 11 inclusive, at the Hotel Statler, Washington, D. C. All sessions will be open to members of the medical profession in good standing with the American Medical Association. In addition to the scientific sessions, the annual instruction courses will be held September 7, 8, 9 and 10. Full information may be obtained by writing to the American Congress of Physical Medicine, 30 North Michigan Avenue, Chicago 2, Illinois.

The American College of Physicians announces that a limited number of fellowships in medicine will be available from July 1, 1949 to June 30, 1950. These fellowships are designed to provide an opportunity for research training either in the basic medical sciences or in the application of these sciences to clinical investigation. They are for the benefit of physicians who are in the early stages of their preparation for a teaching and investigative career in internal medicine. The stipend will be from \$2,200 to \$3,200.

Application forms are obtainable from The American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa., and must be submitted in duplicate not later than November 1, 1948. Announcement of the awards will be made as promptly as is possible.

Grants of more than \$121,000 in Federal funds for research in cancer, allotted among the University of California, Stanford University and the College of Medical Evangelists in Los Angeles, were approved last month by the Advisory Cancer Council and the U. S. Public Health Service. The University of California Medical School in San Francisco received \$85,064, Stanford University \$11,134, the College of Medical Evangelists \$17,419, the University of California in San Francisco \$5,535 and the University of California at Berkeley \$3,419.



# INFORMATION

## Practice of Medicine by Private Nonprofit Hospitals Held Illegal

Recently, the State Board of Medical Examiners requested the opinion of Fred N. Howser, Attorney General of California, as to whether a private nonprofit hospital is permitted by law to practice medicine, and, if not, as to whether such a hospital could legally employ a pathologist on a salary basis.

On May 19, 1948, the Attorney General rendered an opinion to the State Board of Medical Examiners, holding, first, that a private nonprofit hospital may not practice medicine, and, second, that the employment on a salary basis of a pathologist by such a hospital would constitute the unlawful practice of medicine by the hospital.

The opinion, in full, follows:

**OPINION of**  
Fred N. Howser, Attorney General  
E. G. Funke, Deputy Attorney General

The Board of Medical Examiners has submitted the following questions:

1. Is a corporation or an association of laymen operating a private, nonprofit hospital permitted to practice any system or mode of treating the sick or afflicted in this State?

2. If a corporation operating a private, nonprofit hospital enters into a contract with a physician under which the physician will perform professional services in the hospital and receive a fixed salary, and the corporation will thereupon bill the patient for the professional services rendered by the physician at rates that have no bearing on the physician's salary, is the corporation violating any of the provisions of the Medical Practice Act?

The conclusions reached are summarized as follows:

1. No one is permitted to practice any system or mode of treating the sick or afflicted in this State unless he is licensed in accordance with the provisions of section 2000 et seq., Business and Professions Code. Corporations or other artificial legal entities are specifically mentioned in section 2008 as having no professional rights, privileges or powers, and may therefore not be licensed to so practice.

2. The employment of a licensed physician by a corporation and the subsequent billing of the patients by the corporation, as referred to in the second question, would constitute illegal practice of a system or mode of treating the sick or afflicted in this State and is therefore prohibited by law.

### ANALYSIS

The Board of Medical Examiners advises that a private, nonprofit hospital operating in the State and owned by a corporation, contemplates entering into

a contract with a duly licensed physician and surgeon who specializes as a pathologist. They propose that the physician and surgeon will perform professional services for hospital patients and receive therefor a fixed salary. The corporate owner of the hospital proposes to separately bill each private patient for the professional services that have been rendered to such private patient by the pathologist. They propose that such charges are to be independent of the ordinary regular charge for hospital bed, board and usual hospital services and further, that the rate of charge will have no bearing on the salary that the pathologist will receive from the corporation.

The courts have made it abundantly clear, as is hereafter shown, that corporations are prohibited from engaging in the practice of any system or mode of treating the sick or afflicted in this State. The pronouncements of the courts also, in our opinion, require the conclusion that the arrangement contemplated by the hospital in question falls within the same prohibition.

The California Legislature has enacted a Corporations Code. In the Corporations Code there are found various provisions governing the formation, powers and duties of corporations as a whole. Since a corporation is a "creature created by statute," it has only such powers as the statutes give to it. Nowhere in the Corporations Code is a corporation given specific authority to practice the healing arts.

We must, of course, call attention to the fact that certain nonprofit corporations may be formed for the purpose of defraying or assuming the cost of professional services of licentiates of the healing arts. Section 9201, Corporations Code, formerly Section 593(a) Civil Code, so provides. However, the same section except as expressly permitted therein does not authorize the formation of any corporation for the purpose of rendering the professional services regulated by Division 2 of the Business and Professions Code. Likewise, Chapter 1 of Division 2 of the Health and Safety Code, governing the operation of clinics and hospitals, specifically provides (section 1214) that the provisions of said chapter do not authorize any person other than a licentiate of a healing art to engage *directly or indirectly* in the practice of medicine.

The opinion of the Supreme Court in California Physicians' Service v. Garrison, 28 Cal(2d) 790, construed the provisions of Corporations Code 9201, formerly Civil Code 593(a), and particularly the authorizing of the incorporation of a physicians' service. The court therein states (page 802): "The Legislature, by enacting section 593(a) of the Civil Code, expressly authorized the organization of cor-

porations such as California Physicians' Service. By this enactment *the state's social policy in regard to the corporate practice of medicine, to the limited extent specified, has been determined* and the courts are bound thereby. [Emphasis added.]

Further, a corporation, although considered by law as a legal entity, and to have in many respects all the rights and privileges of an individual person, nevertheless is physically unable to fulfill the educational requirements or to take the examination required of all persons who seek to secure a license to practice the healing arts. Thus, even though section 2008, Business and Professions Code, did not specifically state that a corporation has no professional standing, nevertheless it would be a physical impossibility for a corporation to be a licentiate of a healing art.

Our courts have on numerous occasions held that a corporation may not engage in the practice of medicine. The opinion of the Supreme Court in *Pacific Employers Insurance Co. v. Carpenter*, 10 Cal. App. (2d), 592, 594, contains a comprehensive discussion which is pertinent. The following quotation summarizes the court's views on this subject:

"It is well settled that neither a *corporation nor any other unlicensed person or entity may engage, directly or indirectly, in the practice of certain learned professions including the legal, medical and dental professions.* [Cases cited.] Under the foregoing authorities it is clearly declared unlawful for a corporation to indirectly practice any of said professions for profit by engaging professional men to perform professional services for those with whom the corporation contracts to furnish such services. In other words, said authorities declare that said professions are not open to commercial exploitation as it is said to be against public policy to permit a 'middleman' to intervene for profit in establishing the professional relationships between the members of said professions and the members of the public." [Emphasis added.]

In *People v. Pacific Health Corporation*, 12 Cal. (2d), 156, 158, the court stated that: "It is an established doctrine that a corporation may not engage in the practice of such professions as law, medicine or dentistry." [citing cases.] The appellant, Pacific Health Corporation, contended, however, that it did not itself undertake to perform medical services, but merely to furnish competent physicians; that the physicians and surgeons were not to be employed by it on a salary basis, nor directed by it, but were to be compensated for actual professional services after they were rendered; and the corporation's theory was that the doctors, under its arrangement, were to be independent contractors and that, therefore, the corporation would be absolved of the charge of practicing medicine. The court said:

"We are unable to agree that the policy of the law may be circumvented by technical distinctions in the manner in which the doctors are engaged, designated or compensated by the corporation. The evils of divided loyalty and impaired confidence would seem to be equally present whether the doctor received benefits from the corporation in the form of salary or fees. Any freedom of choice is destroyed, and the elements of solicitation of medical business and lay control of the profession are present whenever the corporation seeks such business from the general public and turns it over to a special group of doctors."

This argument that the mere ownership of a hospital where medical services are rendered by the owners' licensed employees does not in itself constitute the practice of medicine (i.e., that the practice of medicine involves actual treatment of persons), was also rejected by our courts when applied to the practice of dentistry. See *Painless Parker v. Board of Dental Examiners*, 216 Cal. 285, 296. Appellant in that case contended that there was a distinction between the practice of dentistry which the statutes undertook to regulate, and the purely business side of the practice and that the management and conduct of the business side by a layman was not prohibited by the statute, and that such attempted prohibition would be unconstitutional. We refer to the well considered opinion of the court, wherein are given the reasons for the rejection of this contention made by appellant.

It may be contended that the pathologist in the situation presented would merely examine and diagnose an illness and therefore would not be practicing medicine. But our courts have held that diagnosis is as much a part of the practice of medicine as is the administration of remedies. In fact, section 2141, Business and Professions Code, declares that one who diagnoses any illness is engaging in the practice of medicine (see *People v. Jordan*, 172 Cal. 391).

Throughout the opinions cited one will note that the courts have indicated that the practice of medicine by corporations for profit, through the employment of licensed physicians, has a tendency to debase the profession, is not in the interests of the safety, health and welfare of the public, and therefore is contrary to public policy. The right to practice medicine and surgery under a license by the State is a personal privilege. It cannot be delegated. Therefore, a corporation or other unlicensed person may not engage in the practice of medicine by employing one who is licensed to do the things which constitute the practice of the profession. Were the rule otherwise, one would find a licensed physician accepting directions and instructions in the diagnosing and treating of ailments from a corporation or from an individual who is not a licensed practitioner.

## BOOK REVIEWS

**LABORATORY TECHNIQUE IN BIOLOGY AND MEDICINE.** By E. V. Cowdry, Professor of Anatomy, Washington University, and Director of Research, The Barnard Free Skin and Cancer Hospital, St. Louis, Missouri. Pp. 269. Williams and Wilkins Company, Mt. Royal and Guilford Avenues, Baltimore 2, Maryland, 1948. Price, \$4.00.

Under the present title, this book is the second revised edition of the author's former book entitled *Microscopic Technique*. It is an alphabetically arranged compilation of qualitative and quantitative micro-tests and techniques applicable to tissues, organs, body fluids, unicellular organisms, bacteria, etc., useful in routine diagnosis, physiological research, microscopic study, toxicological examinations and other laboratory work. No detail has been overlooked. The techniques described are of proved value and most of these were revised by their originators. Sufficient detail is given to enable an experienced person to proceed without difficulty. Many references to original papers for further details are included. When micro-technique is not applicable, other procedures are suggested, for instance, use of a spectrophotometer or spectrograph, etc. Outstanding is a lengthy and detailed description of Knisely's quartz rod technique for examining living organs *in vitro*, especially the capillary circulation, a valuable method in a wide variety of physiological problems. All in all this edition is remarkably complete in content and scope. It is a must for hospital technicians, researchers in biological and medical sciences and clinical pathologists.

**ENCYCLOPEDIA OF MEDICAL SOURCES.** By Emerson Crosby Kelly, M.D., F.A.C.S., Associate Professor of Surgery, Albany Medical College, attending surgeon, Albany Hospital, Editor, *Medical Classics*. The Williams & Wilkins Company, 1948. Price, \$7.50.

The author has made available an informative volume not only for those who are interested in medical history, but also for those who desire precision in regard to medical eponyms. At the same time he has compiled a magnificent bibliography of the important contributions to medicine and surgery for those who wish to write papers for the clinician. The volume constitutes an indispensable repository of fundamental bibliographic information and makes possible for writers the saving of untold hours of library research. The author puts upon a sound historical and bibliographic basis the true but often falsely quoted works of the great clinicians, whose original and pertinent references are made easily available. For those who find the dictionary enjoyable reading, "The Encyclopedia of Medical Sources" will offer similar entertainment although it was originally intended as a source book.

**PROCEDURE IN EXAMINATION OF THE LUNGS.** Kraetzer, Third Edition, Oxford Medical Publications. 1947. \$3.50.

This book has long been a most valuable aid to the student in becoming oriented on the chest, something which many graduates have never learned. It has also served to emphasize a phase of examination which there has been a tendency to ignore since the more recent refinements of roentgenography and the emphasis on its peculiar value in the diagnosis of early tuberculosis. We have heard not a few papers and discussions minimizing or ignoring the physical examination of the chest in this connection, overlooking the fact that there are a number of conditions in which the x-ray gives us no information. In his enthusiasm for mass surveys the tubercu-

losis clinician is at times prone to lose sight of the fact that the purpose of the examination is to detect any pathological condition in the patient's chest, not simply whether he has tuberculosis or not. Bronchitis, bronchiolitis, asthma and beginning bronchostenosis from tuberculosis or other cause are only a few of the conditions whose recognition is not helped by the x-ray.

It is, however, disappointing to find some of the omissions of the former editions carried forward into this one. Failure to mention the heart in the chapters dealing with inspection and palpation is one of the minor but obvious deficiencies. The continuation of some outmoded findings such as Kroe-nig's isthmus is also unfortunate.

The discussion of the causes of spontaneous pneumothorax is in need of revision.

Dr. Segal contributes a very valuable appendix in an attempt to bring the book up to date.

It is obvious that the addition of an appendix, however good in itself, is not sufficient justification for calling this a new edition. It is to be regretted that a firm with the standing of the Oxford Medical Publications should be guilty of such a breach of faith with its clientele, a practice which is bound to react unfavorably on its reputation in regard to future publications.

**THE LUNGS.** William Snow Miller, M.D., F.C.D. Sc. Second Edition. Charles C. Thomas, Springfield, Ill. \$7.50.

Ever since the first edition of this book appeared in 1937 it has been the vade mecum for those who would understand the physiology and pathology of the lungs. Those whose small individual financial contributions made possible the summarizing of the lifetime work of the author are entitled to feel a degree of pride in the presentation which has been achieved.

Within the limits of a book of this size it has not been possible to incorporate all his work. This edition, which contains an added number of color plates, black and white illustrations and manuscripts, is to that extent an improvement on its predecessor. It is hoped that still more may be included in a future revision.

The outstanding quality of the color plates of the first edition has been well maintained in the second.

**PRACTICAL METHODS IN BIOCHEMISTRY.** Fifth Edition. F. C. Koch and Martin E. Hanke, University of Chicago, pp. 419, ix prelims. Williams and Wilkins Co., Baltimore, 1948. Price, \$3.00.

This book is a happy compromise between one widely used laboratory guide of 1,321 closely printed pages and another of 149 pages. Since the three books endeavor to serve the same end and, indeed, carry virtually the same title, somewhat of a comparison may be worth while. Both the "Fat" and the "Thin" contain sections on Mili and Epithelial and Connective Tissues. Koch and Hanke chose to omit these, and wisely so, in the judgment of the reviewer; the experiments usually performed on these materials are dull, uninformative, and seldom illustrate any point of fundamental importance. "Fat" contains a good section on enzymes which, because of its emphasis on general enzyme biochemistry, is a good prelude to the chapters on digestion and might well be included in other good laboratory manuals in biochemistry. Koch and Hanke included, of course, the usual chapters on digestion and did so quite concisely in about half the space. The authors devoted 145 pages to blood and urine

in contrast to the 73 pages in "Thin" and the 392 pages in "Fat." Koch and Hanke's book is a straightforward, practical laboratory manual, while "Fat" is, admittedly, a substantial reference book as well. In the reviewer's opinion, Koch and Hanke have turned out a thoroughly good manual in which the subject matter is well balanced as to division of space. The book has run through four previous editions and, hence, is almost free of typographical errors (*steriod* on page 347 and *untable* on page 65). It contains two excellent chapters, totalling 50 pages of experiments, on Vitamins and Microbiological Assays. These are very timely subjects and, as far as the reviewer knows, are not to be found in any other laboratory book intended for the introductory student of biochemistry.

The appendix describes in greater detail than does its fat companion the preparation of the numerous reagents required for laboratory instruction in biochemistry. It is unfortunate that it does not contain, as does the larger work, a section on the maintenance of laboratory animals for experiments in nutrition. Such material reminds the student of our indebtedness to the rat, the guinea pig, etc. and indicates to those who enter upon the study of medicine the fundamental importance of animal experimentation in medical research.

The book is not without its other faults but to the reviewer, they are comparatively few and, in some cases, trivial. As in almost all laboratory manuals an experiment is to be found on the Lobry de Bruyn and van Ekenstein rearrangement. Fortunately, the authors do not suggest that this is of any biological significance; to minimize the possibility of concluding, by implication, that fructose and mannose are by this means converted to glucose, *in vivo*, it would be well in future editions to mention the role of phosphorylation in effecting the fructose-to-glucose conversion.

In the determination of nitrogen in blood and urine, emphasis is given to direct Nesslerization methods. With sufficient practice, and when employed by experienced technicians, these methods may be used with confidence. The reviewer, however, has seldom found that they were satisfactory for the usual large class of medical students: a gross precipitate or a troublesome opacity frequently develop on Nesslerization. Since rapid, accurate, semi-micro, Kjeldahl and steam-distillation methods are readily available, these are to be preferred, in the reviewer's opinion, for the determination of urea, total nitrogen, and non-protein nitrogen.

In many instances the authors offer a choice of methods. They do so usually without appraisal and without giving to the reader the benefit of their years of experience in biochemistry. This fault is not peculiar to the book by Koch and Hanke, for seldom indeed does it happen that analytical methods are presented in laboratory manuals on biochemistry according to any rating system.

The text contains a few curious constructions which may disturb a grammarian insistent upon purity of syntax. For example, on page 39, should not the phrase "dissolve this in a test tube in about 6 cc. 95 per cent alcohol" be changed to read "dissolve this in about 6 cc. of 95 per cent alcohol contained in a test tube"? On page 115 we read "the pH's appear too acid." Surely this should be "the pH's appear too low" or "the solutions appear too acid."

"Saccharose" is used throughout the text in place of "sucrose" except on page 143, where, for no apparent reason, the much more popular "sucrose" comes into its own.

There are many needless inconsistencies in the printing of chemical names which suggest the need of more careful editing in future editions:

On page 53 we find "para-dimethyl-amino-benzaldehyde" but on page 373 "dimethyl-amino-benzaldehyde," "p-dimethyl-amino-benzaldehyde" and "p-dimethylamino-benzaldehyde"—all three versions within the space of six lines. Both

"chromotropic acid" and "chromotrophic acid" are to be found on page 79. The adjective "colorimetric" is singled out, without apparent reason, for capitalization on page 81. Alphanaphthol and  $\alpha$ -naphthol appear together on page 382, and tyrosine and tyrosin on page 407.

All in all this is an excellent book and will be found useful by clinical technicians, research assistants, and medical students.

Professor Koch passed away while this present edition was in press. The book testifies to his many years of work in biochemistry, to his excellence as a teacher, and to his insistence upon precision and meticulous care in laboratory technique.

**OCCUPATIONAL MEDICINE AND INDUSTRIAL HYGIENE.** By Rutherford T. Johnstone, A.B., M.D. Consultant in Industrial Health; Lecturer at the University of California, Los Angeles. Formerly Assistant Professor of Medicine, University of Pittsburgh School of Medicine. With One Hundred Seventeen Illustrations, Seven in Color. The C. V. Mosby Company. 1948.

As mechanization of our civilization has progressed, there has been a growing need for books describing and explaining the diseases arising from occupational exposures. Expanding knowledge of chemistry and physics has made possible the economical preparation of new materials and of new agents for processing familiar materials. Even in the home, strange compounds are becoming common: detergents are often not soaps, dishes are often not crockery, cleansing solvents not gasoline, adhesives not glue. In industry, not only manufacturing, but also agriculture and the service industries, the introduction of unfamiliar compounds is even more pronounced. Most of these novel materials are harmless, and in many instances they have been tested adequately to demonstrate this, but the practicing physician needs a better way of finding out which ones are potentially dangerous than by writing to *Queries and Minor Notes* of the J.A.M.A.

Moreover, California industrialists are becoming increasingly aware of the potential benefits of in-plant medical services. One factor retarding the greater utilization of medical knowledge by industry is the lack of preparation by physicians to take an effective, leading part in this endeavor.

In any attempt to cover this broad and changing field, the breadth and variety of topics to be considered is formidable. Previous authors have dealt with the problem by editing symposia or by very extensive quotations from various sources. This has almost inevitably led to imperfect balance of emphasis and lack of integration of the several contributions. Dr. Johnstone has written his own book, with the good result that each of its parts is well related to the whole. He has been free with his use of quotations, but he has made them part of his own work by discriminating choices and critical evaluation. The outcome is the best book ever written in this field. It is not a mere revision of Dr. Johnstone's previous work, *Occupational Diseases*; while retaining the best features of that book and bringing the material up to date, he has made a new and more effective approach to the problem of engendering understanding of occupational disease through more detailed and clearer explanations of the underlying processes by which noxious materials are taken into the body and absorbed, and the physiological and anatomical changes which result. He has added a section on industrial hygiene.

One of the best things about this work is the forthright, positive attitude of the author. He is not one to hedge about his opinions with ambiguous qualifications. Consequently, there are a number of points about which there is room for disagreement, but all the major premises are sound, and it is refreshing to read a medical text which reflects something of the author's personality.

The range of topics is from a broad consideration of the character of occupational medicine and industrial hygiene to detailed reports of cases of accidental intoxications. The opening chapters discuss the place of industrial medicine in the body of medical practice, the background of workmen's compensation laws and their relation to medical practice, and the importance of thorough study and accurate reporting in medicolegal cases. There is invaluable practical advice on the preparation of reports. After further generalizations on the functions of the industrial physician, the teaching of industrial medicine, the basic approach to a diagnosis of occupational disease, and a summary of useful laboratory procedures, the various noxious agents (solvents, metals, dusts, and so on) are treated categorically and individually. The nature of the agent, its uses, its effects in the body, the symptomatology, diagnosis, and treatment of poisoning are described and illustrated by appropriate case reports. Finally, after describing some industrial techniques of special interest, methods of protecting health of workmen, based on the materials covered before, are presented briefly, but sufficiently in detail to have practical value. There are many excellent illustrations, and several tabular summaries.

In all of this, especially in the case reports, the author's long and varied experience shows its value. There is no other book so likely to have the answers the doctor seeks when he must decide on the part played in an illness by the patient's work, or when he looks for methods of treatment and measures for protection from repeated exposure to occupational hazards.

**PATHOLOGICAL HISTOLOGY.** By Robertson F. Ogilvie, M.D., F.R.C.P. (Edin.), F.R.S.E., Lecturer in Pathology and Assistant in Forensic Medicine, University of Edinburgh, Third Edition with 260 Photomicrographs in Colour. The Williams and Wilkins Co. 1947.

Teachers of pathology agree that no perfect textbook on the subject exists, and this book is no exception. However, in the preface, the author specifically states that the book is designed to act as a companion to a standard textbook of pathology. In this respect, this book definitely fulfills its author's aims, and should be of considerable value to students of pathology.

For a complete understanding of morbid processes in tissues, the student needs detailed knowledge of the histologic changes occurring in various diseases. It is in this phase of the study of pathology that this book may assist the student in examination of sections under the microscope.

This third edition systematically considers in a text of 447 pages the pathologic lesions of most of the common disease processes. Each disease or pathologic lesion is defined briefly in an introductory paragraph, which includes a short discussion of factors of etiology, classification, and correlating clinical data. Then each lesion or process is described macroscopically and microscopically in concise but thorough manner. These excellent descriptions are accompanied by 260 photomicrographs in color. To a pathologist and a photomicrographer they are well chosen, technically excellent and beautifully illustrate the descriptive text.

In only a few instances is the terminology different from that in most American textbooks, and these differences are not confusing. In the section on hepatic disease, the author's grouping of all types of cirrhosis under the heading "Common Cirrhosis," will be approved by few investigators in the field of hepatic disease and cirrhosis.

**NURSING IN MODERN SOCIETY.** By Mary Ella Chayser, R.N., M.A. Published by G. P. Putnam Sons, 1947. \$4.00.

This publication includes three parts: Part One, The impact of social forces on nursing; Part Two, The influence of social forces upon community health needs; Part Three, Building a better future.

The reasons for the industrial revolution are discussed as are the relation of capital and labor, urban migration, family life, medical care under voluntary insurance plans and by compulsory governmental legislative action.

Nursing is described as a social force and legislation is advocated to insure its place as such. The program of the National Nursing Council is outlined, as is the organization of the Joint Committee on Auxiliary Nursing. Personnel policies on collective bargaining for nurses receive attention. Special consideration is given to the organization of various nursing bodies. Raymond Rich Associates have been employed as technical consultants to these bodies, to advise on details of organization of professional nurses and on the legal steps to be taken to accomplish their ends.

The view is expressed that nursing should be an autonomous profession and that this is the time to make it so. The professional nurse is considered the one to define properly the functions of medical social workers, physical therapists and practically all hospital personnel. Direction of various types of hospital personnel is seen as appropriately under the direction of the professional nurse rather than under the direction of medical staff or hospital superintendent. Recent surveys have shown the medical profession to be aware of such aims on the part of those in control of organized nursing—and to be aware also of a deterioration in the quality of the nursing care of the sick. The same surveys reveal agreement on the one hand that nurses are underpaid, and on the other that the cost of special nursing is prohibitive to the average patient, and agreement too that vocational nurses, after short periods of training, are able to furnish the care most needed by patients. The training of such a group in our nursing schools, however, is opposed by the central nursing organizations and in our private hospitals a closed shop prevails against practical nurses.

"Nursing in Modern Society" promotes the concept that the nurse is a social agent, and that she must organize and legislate. It expresses the aims of the central nursing bodies, dedicated to developing a profession independent of the medical profession, not an auxiliary to it. It advocates taking over many of the functions of the medical profession as well as independence from it.

We need another Florence Nightingale to redirect the trend of nursing. The heart seems to have gone out of it.

**THE DISSECTION OF THE CAT (Felis Domestica)—A Laboratory Manual.** By Bruce M. Harrison, Ph.D., Professor of Zoology and Head of the Department, The University of Southern California, Los Angeles, California. The C. V. Mosby Company, St. Louis. 1948. \$3.50.

As the title of this manual suggests it is a laboratory outline for premedical students with good pen and ink drawings that are to be labeled by the student.

Some of the questions at the end of the chapters are on comparative anatomy. Three illustrations of the anatomy of man are used to compare with that dissected in the cat.

It should be an excellent guide for the premedical and prenursing student.

**HANDBOOK OF FRACTURES.** By Duncan Eve, Jr., M.D., F.A.C.S., Surgeon and Chief Nashville, Chattanooga and St. Louis Railroad. The C. V. Mosby Co., St. Louis. 1947. \$5.00.

The handbook is an excellent portrayal of many years' experience and careful work on fractures by a man conversant with modern principles of fracture treatment. As such, it is valuable to the specialist in this field.

The author has expressed the hope that the handbook will be helpful "to the younger and more occasional worker in the field." The handbook would be of value to such a man, if he also has at his disposal a good two-volume treatise on

fractures. The fact remains that the less a doctor knows about a subject the more he needs to rely on books and the experiences of others.

**INTRODUCTION TO HUMAN PHYSIOLOGY.** By William D. Zoethout, Ph.D., Professor Emeritus of Physiology in the Chicago College of Dental Surgery (Loyola University). 138 Text Illustrations and 4 Color Plates. The C. V. Mosby Company, St. Louis, 1948. \$4.00.

This book was designed for "the reader desirous of obtaining a fundamental knowledge of the operation of the human body but having no previous knowledge of the basic sciences of Physics and Chemistry." Like many books addressed to such an audience the present work is both elementary and superficial. Moreover some of the statements found in this book are clearly wrong. Thus on page 257 one finds the surprising and erroneous comment on insulin that, "It is now made synthetically; this greatly reduced its cost." As insulin is a protein and as no protein has yet been synthesized, this mistake implies either carelessness or serious lack of information. On page 48 the production of alcohol and carbon dioxide from glucose by yeast is attributed to an unorganized ferment. This process, as is well known, involves not one but a whole series of enzymes. The discussion on glycolysis (page 77) would lead the reader to consider lactic acid a key substance in carbohydrate degradation instead of the by-product which the work of Meyerhof and others has shown it to be. The book as a whole impresses the present reviewer as labored and uninspired. It cannot be recommended to any reader who desires a discussion of the fundamentals of physiology which is illuminated by intelligence and insight.

**TEXTBOOK OF GYNECOLOGY.** By Emil Novak, M.D., F.A.C.S., Assistant Professor of Gynecology, The Johns Hopkins Medical School; Third Edition. The Williams & Wilkins Company. 1948. \$8.00.

While the Textbook of Gynecology by Emil Novak is designed primarily for the student and practitioner, a trained Gynecologist will enhance his knowledge tremendously if he reads this well planned third edition. Elimination of operative technique makes possible a comprehensive treatise of the entire subject in some 500 pages of written material. Original illustrations, as well as those borrowed from other authors, depict the lesions and further embellish the descriptive material. The color photography is outstanding.

The chapters on cancer, adenomyosis, myomas and diseases of the vulva are particularly valuable. To the reviewer they best exemplify Dr. Novak's ability to correlate, clarify and summarize a large amount of material without losing any important factors. If you have heard the author speak on these subjects, it brings to mind the pleasant, stimulating conversational style which few teachers possess.

In two short paragraphs the vaginal smear method of diagnosis is carefully evaluated and will give the practitioner an answer to the patient who comes for "the simple test of diagnosing cancer," as publicized by the lay press.

In the discussion of total versus supravaginal hysterectomy on page 322 I quote, "The long continued discussion as to the relative advantages and disadvantages of the two techniques has pretty well crystallized in the viewpoint that the total operation is the one of choice, and it should be selected unless there is present some contraindication imposed by the local conditions in the case of great obesity, unusually deep pelvis, fixation of the uterus by extensive pelvic endometriosis or pelvic inflammatory diseases, or by the surgical limitations of the operator. In my own work, something like 75 per cent of hysterectomies are of the total variety." This seems to summarize in a concise, critical and unbiased manner the opinion of Gynecologists of the present day.

For therapy, the chapter on the menopause and the general discussion of gynecological organotherapy should discourage physicians who resort to the use of "shots" for every conceivable alteration of menstrual function and the associated vasomotor symptoms.

This book is a monumental volume to the author's ability and should be available in every medical library, both public and private, worthy of the name.

**MENTAL HEALTH, A Practical Guide to Disorders of the Mind.** By John H. Ewen, F.R.C.P.E., D.P.M., Physician and Lecturer in Psychological Medicine, Westminster Hospital; Medical Superintendent, Springfield Mental Hospital, London; Formerly Examiner in Psychological Medicine, Royal College of Surgeons, England. With a Chapter on Special Treatments and Their Practical Technique, by C. Friedman, M.D., (Vienna), L.R.C.P.&S., Ed., Registrar and Tutor, Department of Psychological Medicine, St. Thomas's Hospital. Psychotherapist, The Tavistock Clinic. Medical Officer, Insulin Therapy Clinic, Springfield Mental Hospital. The Williams & Wilkins Company, Baltimore, 1947.

The authors have written along lines of a textbook on psychiatry, with much more emphasis upon the diagnosis and treatment of the psychotic states with which they have apparently had more experience. The young physician who is entering institutional psychiatric work will find it more useful than the doctor who would prefer more psychological insight into the emotional problems of the patients he sees in his everyday practice. Comparatively little space is given to the discussion of the psychoneuroses, and almost none to the general conceptions of psychosomatic medicine. The chapter on "Specialized Treatments and Their Technique" includes descriptions of electrical convulsion treatment, insulin therapy, malarial therapy, prefrontal leucotomy, continuous narcosis, and narco-analysis, and this is concisely written and, on the whole, quite adequate in presentation. The conditioned reflex treatment for chronic alcoholism might have been included here, but apparently this method has not achieved the popularity it has assumed in the United States.

More emphasis upon the psychodynamic formulation of psychological disorders would have helped to improve this text. Such a statement as "Emotional shock considered from the organic viewpoint is a form of auto-intoxication and may produce the same effects on the mental life as the organic shock resulting from fevers and poisons" needs further elaboration. The author considers lactation an "exhaustive state," and the psychoses occurring during and after pregnancy as "organic reaction types of mental disorder," although he states "possible psychogenic factors must receive adequate consideration." This is still a controversial problem, but there is accumulating a large body of evidence indicating that psychological factors play a considerable role in the mental illnesses associated with pregnancy and the post-partum period. Most authorities would disagree with the author's statement that "epilepsy considered from the mental point of view is a progressive disorder culminating in terminal dementia." This might be true of some of the institutionalized epileptics, but these constitute only a small percentage of the large group of extramural epileptics. Such a fatalistic point of view would deter therapy which would prove so useful in this disorder. The section on "Legal Aspects of Mental Disorder" refers primarily to British law, much of which is not relevant to the practical problems with which the physician must deal in this country, although there is much of a general character in the principles laid down which could prove useful to the reader.

This book cannot be recommended as providing an adequate description on modern concepts in psychiatry because of its lack of presentation of the details of psychodynamic formulations of emotional problems.

## MEDICAL JURISPRUDENCE

PEART, BARATY & HASSARD *of the California Bar*

A recent decision by the California District Court of Appeal (85 A.C.A. 251, May 7, 1948) involving a discussion of the doctrine of *res ipsa loquitur* may be of interest to physicians and surgeons.

The District Court of Appeals had before it a case arising from the following facts: At the trial the plaintiff patient testified that she had been suffering from a varicose vein condition in both legs from her thighs to her ankles. The defendant doctor made a visual examination of the patient and directed that she enter a hospital. While in the hospital the physician examined patient's legs again and then directed a hospital nurse to bring him a small basin of water and a silver nitrate pencil. The physician then dipped the pencil into the water and outlined the patient's leg veins that were to be removed. There were four of such markings made on each leg, two above the knees and two below. The plaintiff patient testified that shortly thereafter her legs began to burn and became very inflamed around the areas marked by the defendant, and that in a short time blisters formed at such areas. The defendant physician was unable to operate the next morning as had been planned, and upon examination of the patient's legs told her that the operation could not be performed because the burns were too severe. As a result of these burns, the plaintiff testified, she was forced to remain away from work and had to wear bandages for over a month, and she testified that she was still scarred from the burns.

The only other witness was the defendant physician himself, who testified that in his city it was the common practice of physicians in this type of operation to mark off with a silver nitrate solution the area to be operated upon, and that it was also standard practice in his area to mark off the operating area without first making any tests. He stated that prior to his treatment of plaintiff he had performed three or four hundred of such operations and that everything he did in this case was performed according to the ordinary standards of practice of surgeons in his city.

On this evidence the trial court granted the defendant physician's motion for a non suit on the ground that the plaintiff had failed to show that the defendant physician did not possess and use the degree of skill possessed by other practitioners in the same locality.

On appeal the District Court of Appeal stated that the trial court was correct in granting the non suit unless the doctrine of *res ipsa loquitur* was applicable.

In its opinion the court stated that the doctrine normally applies where the accident that occurred was such that in the ordinary course of events the defendant using ordinary care, it would not have happened, and where the instrumentality causing the accident was under the control of the defendant. In an analysis the District Court of Appeal held that all of the requirements of this doctrine had been met and therefore this operated to raise an inference of negligence and the trial court, it stated, should not have granted the non suit.

It may be noted in this opinion that a dissent was entered by one of the Justices of the District Court of Appeal in which he stated that negligence upon the part of a physician or surgeon is not presumed from the mere happening of an injury to a patient under his care. Further, that the doctrine of *res ipsa loquitur* should not be extended to the point where negligence from the mere happening of an injury to a patient might be presumed. In his analysis the dissenting Justice states clearly that the law has never held a physician or surgeon liable for any untoward result which may occur in medical practice. It requires only that he shall have the degree of learning and skill ordinarily possessed by physicians of good standing practicing in the same locality, and that he shall use the ordinary care and diligence in applying that learning and skill to the treatment of his patients. From this the dissenting Judge concluded that the facts did not warrant the application of the doctrine of *res ipsa loquitur* and, therefore, the judgment by the lower court should have been upheld.

